(DIS-)INHIBITORY GATING OF EXCITATORY SYNAPTIC PLASTICITY:
a cellular modeling approach

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Für meine Eltern.

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Abstract

The neuronal correlate of learning is thought to be the experience-dependent adjustment of neuronal connections – synaptic plasticity. However, cellular processes mediating these changes are highly regulated, and can e.g. be influenced by the state of the organism. Limiting learning to behaviorally relevant episodes is for instance useful if new experiences can overwrite old memories. In this thesis, we use computational modeling to explore a mechanism by which cellular processes for learning (happening in the principal neurons of the brain) can be modulated by another cell type: local inhibitory neurons. Although these cells are known to play a role for learning, the cellular mechanisms by which they could influence synaptic plasticity are not completely understood. The aim of this thesis is hence to shed light onto the cellular mechanisms underlying the regulation of synaptic plasticity.

In the first part of this thesis, we show that inhibitory neurons can modulate signals for plasticity in the dendrites (input structures) of principal neurons in an all-or-none manner. Thereby, inhibition can provide a binary switch for plasticity, which – as we further demonstrate – can be specific for inputs arriving via different neural pathways. An important dendritic signal for synaptic plasticity is the backpropagating action potential; the neuron fires an action potential that travels along the axon to the next neuron and additionally travels backwards into the dendrite (hence backpropagating action potential). This backward-directed signal informs synapses about the activity of the neuron and can be modulated by inhibition. We show that the timing requirement for inhibition of backpropagating action potentials is tight; especially if modulation of plasticity via this mechanism ought to preserve forward-directed stimulus processing from the synapses to the axon in the same neuron. Yet, we demonstrate that the desired timing can be accomplished if inhibition is embedded in a common neuronal network motif: an inhibitory feedforward circuit.

In the second part of this thesis, we address the question whether and how appropriately timed inhibitory feedforward circuits can be established in the brain. We propose that *spike-timing dependent plasticity* (plasticity that depends on the relative timing of activity in the connected neurons) at inhibitory synapses can shape microcircuits to become properly adjusted to the individual timing requirements of the modulated principal neuron. For this purpose, we propose particular inhibitory plasticity rules and demonstrate their functioning.

Zusammenfassung

Verbindungen zwischen Neuronen in unseren Gehirnen verändern sich abhängig von unseren Wahrnehmungen und Erlebnissen. Diese ständigen Anpassungen der Verschaltungen – synaptische Plastizität genannt – ermöglichen uns Erlebtes zu erinnern und daraus zu lernen. Die zellulären Prozesse, die diese Veränderungen herbeiführen, werden stark reguliert, und können beispielsweise durch den Zustand des Organismus beeinflusst werden. Diese Doktorarbeit befasst sich mit der Ergründung eines Mechanismus durch den zelluläre Prozesse des Lernens, die in den häufig vorkommenden Pyramidenzellen stattfinden, durch spezielle, lokal hemmende Neurone moduliert werden können. Dazu werden biophysikalische Modelle einzelner Zellen in Mikroschaltkreisen zu Rate gezogen.

Im ersten Teil dieser Arbeit zeigen wir, dass hemmende Neurone die Lernsignale in den Dendriten (Bereich eines Neurons, in dem Signale von vorgeschalteten Zellen eingehen) der Pyramidenzelle nach dem Alles-oder-Nichts-Prinzip modulieren. Demnach stellen diese hemmenden Neurone einen binären Schalter für das Lernen dar, der, wie wir weiter zeigen, auch Nervenbahn-spezifisch agieren kann. Im Speziellen moduliert dieser Schalter ein wichtiges dendritisches Lernsignal: das rückwärts-gewandte Aktionspotenzial; wenn ein Neuron ein Aktionspotenzial feuert, läuft dieses nicht nur entlang des Axons zur nachgeschalteten Zelle, sondern zusätzlich in die entgegengesetzte Richtung in den Dendriten, wo es Synapsen über die Feueraktivität des Neurons unterrichten kann.

Die Aktivierung der Hemmung muss zeitlich genau erfolgen wenn es um die Blockierung dieses rückwärts-gerichteten Aktionspotenzials geht; dies ist insbesondere der Fall, wenn der betrachtete Mechanismus der Lernregulierung gleichzeitig den vorwärts-gerichteten Informationsfluss erhalten soll. Dennoch können wir zeigen, dass die gewünschte Taktung erreicht werden kann, wenn die hemmenden Neurone in einem häufig vorkommenden neuronalen Netzwerkmotiv eingebettet sind: einem inhibitorischen *Feedforward-Schaltkreis*. In einem solchen Schaltkreis werden die hemmenden Neurone und die Pyramidenzellen von der gleichen vorgeschalteten Zellpopulation erregt, sodass die Pyramidalzelle erst erregende und dann hemmende Reize erfährt, was eine genaue Taktung zwischen Erregung und Hemmung ermöglicht.

Im zweiten Teil der Arbeit befassen wir uns mit der Frage ob und wie solche zeitlich regulierten Feedforward-Schaltkreise im Gehirn etabliert werden können. Wir schlagen vor, dass sogenannte *spike-timing dependent plasticity* (synaptische Plastizität die von der relativen zeitlichen Aktivierung der verbundenen Neurone abhängt) an hemmenden Synapsen diese Schaltkreise so formen kann, dass diese angemessen sind für die individuellen zeitlichen Bedingungen der modulierten Pyramidenzelle. Zu diesem Zwecke, schlagen wir konkrete Lernregeln für hemmende Synapsen vor und demonstrieren deren Funktionsfähigkeit.

Contents

1 Introduction to the thesis

In the first years of their life, children learn to natively understand and speak the languages they are exposed to in stunningly little time. Adults, who want to learn a new language are sometimes frustrated by their own slow progress, having kept the patience of their younger selves, but – for some reason – not their learning ease. However, even though their brains seem to lack childhood flexibility, adults can still learn many skills – no matter how useful. They can also effortlessly form new memories. Learning and memory are thought to be possible, because the brain consists of many individual processing units – *neurons* – that assemble into dynamic networks. Synapses (connections) between neurons in these networks can appear or disappear, and become stronger or weaker within seconds. The dynamic change in connections – *synaptic plasticity* – is guided by experience, and hence allows to learn and memorize the experienced. Given that both young and adult brains are plastic, could synaptic plasticity be more controlled in adults?

A good reason for limiting adult plasticity provides the plasticity-stability dilemma: the problem that stability of memories is at odds with permanently changing synaptic configurations. The older we are, the more we have already learned and the higher is the risk of overriding established synaptic configurations when changing synapses due to new experiences. Ideally, brains should first shape themselves according to the environment, and later only adapt to important new experiences, e.g. those indicating a change in the environment. How can such selective learning occur in adult brains? Neuromodulatory systems that activate during behaviorally relevant conditions such as reward, surprise, or fear, can influence learning. They modulate the plasticity of principal neurons in the brain. But the underlying cellular mechanisms are just beginning to be investigated.

One key player in the modulation of plasticity seem to be local inhibitory neurons – a class of *interneurons* – which inhibit the dendritic trees (the input structures) of principal neurons. Thereby they can suppress signals traveling from the cell body to the synapses in the dendritic tree, so-called *backpropagating action potentials*. These signals indicate to the synapses whether the neuron fires; they are important for forms of synaptic plasticity that rely on coincident action potential firing of the connected neurons: if the coincidence signal is missing, plasticity is disrupted. Hence, inhibition could potentially modulate plasticity by controling backward dendritic signaling. However, normal information processing requires that the input to the neuron – which arrives at the dendritic synapses – flows in the forward direction to the cell body, such that it can cause the neuron to fire (the output). Therefore, dendritic inhibition faces the challenge to block the backpropagating action potential without interrupting forward-directed information flow. One puzzle, we focus on in this thesis is whether and how inhibition can achieve this. Furthermore, inhibition can also modulate other dendritic signals that play a role in plasticity. These signals can be specific for restricted parts of the dendrite.

Hence, one may ask how inhibition affects these signals, and whether inhibition could modulate plasticity on a subcellular level.

Among several others, these questions need to be answered on the way to understand how plasticity can be controled on a cellular level. In the studies of this thesis, we approach these questions by computational modeling of neurons in microcircuits. In particular, we study with these models how inhibition affects backward-directed signaling in dendrites. Ultimately, this thesis elucidates a cellular mechanism for the switch-like and pathway-specific control of plasticity that simultaneously maintains forward information processing, and that can develop in a common circuit motif with initially plastic synapses.

Structure of the thesis

The thesis is structured as follows:

In Chapter 2, I introduce the basics of synaptic plasticity, how it depends on neural activity, and what is known about the underlying mechanisms. I then describe the diverse forms of plasticity modulation, where I distinguish neuromodulation – which may govern the control of plasticity explored in this thesis – from other causes of variations in synaptic plasticity. In particular, I allude to one circuit motif that seems to be capable of plasticity modulation: disinhibitory circuits, which have recently been discovered to play an important role for learning during behavioral paradigms and provide a setting for the cellular mechanisms for plasticity control that we investigate in this thesis. I close the background section by motivating how dendritic inhibition could modulate plasticity on a cellular level.

In Chapter 3, I derive the questions approached in this thesis from previous research on the modulation of synaptic plasticity. I further outline the agenda pursued in this thesis and present our computational approach.

In Chapter 4 (Wilmes, Sprekeler, Schreiber, 2016), we explore the requirements for plasticity control via inhibition of dendritic signals. We show that a subcellular pathway-specific control of these signals and hence plasticity is possible. We find that inhibition of plasticity and information processing are compatible, if inhibition is constrained in time. We further demonstrate that these constraints on timing can be fulfilled by feedforward inhibitory circuits.

In Chapter 5 (Wilmes, Schleimer, Schreiber, 2016), we investigate how the tight timing of inhibition in feedforward circuits can be established. For this matter, we propose an inhibitory plasticity rule that automatically fine-tunes the circuit.

In Chapter 6, I finish with a general discussion, where I relate the thesis to current research and point out which questions remain to be investigated.

2 Background

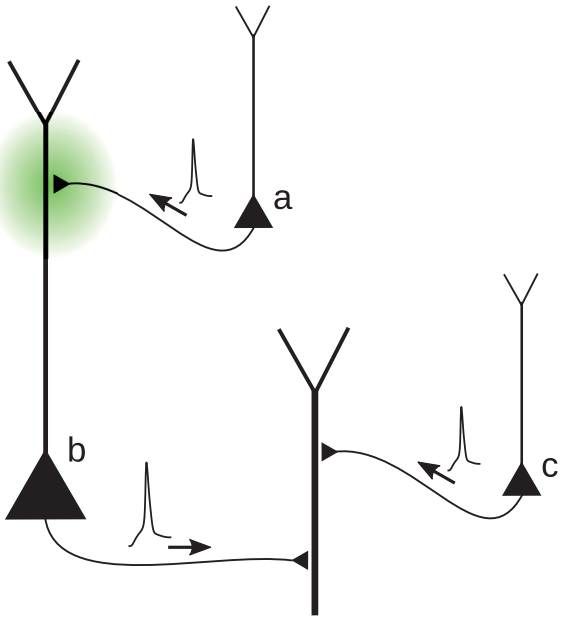

Figure 2.1: **Factors determining synaptic plasticity.** Changes in synaptic strength depend on local activity, i.e. activity of the connected neurons (a and b for the synapse highlighted in green) and less so on the activity of more distant neurons in the circuitry (c in this example).

2.1 Synaptic plasticity

Sensory experience is essential for shaping neural circuits, especially during development (Katz and Shatz, 1996). Rules must exist according to which neuronal activity, which is at least partly driven by sensory stimuli, changes connections between neurons in a circuit. From the perspective of two connected neurons in the circuit (a and b in Figure 2.1), the axonal terminal of the presynaptic neuron (a) meets the dendrite of the postsynaptic neuron (b) and forms a synapse. Activity in the pre- and postsynaptic neurons, or other local factors, can trigger biochemical processes that lead to a change in synaptic strength. For instance, the presynaptic terminal emits neurotransmitters that bind to receptor proteins in the postsynaptic membrane, which in turn activates postsynaptic mechanisms for synaptic plasticity. Hence, rules for synaptic change need to be functions f of local variables available at the synapse, such as pre-and postsynaptic activity, or the strength of the synapse (opposed to activity in distant parts

of the network)

$$\frac{\mathrm{d}w}{\mathrm{d}t} = f(pre, post, w), \tag{2.1}$$

where w is the synaptic strength, $\frac{\mathrm{d}w}{\mathrm{d}t}$ its rate of change, and *pre* and *post* refer to the activity of pre- and postsynaptic neurons.

A simple yet useful rule, for instance, is the 'use it or lose it' principle (Wiesel and Hubel, 1965): strengthen active synapses, presuming they carry relevant (sensory) information, and eliminate inactive synapses (in this case synapses change as some function f of only presynaptic activity: $\frac{\mathrm{d}w}{\mathrm{d}t} = f(pre)$). If the goal of synaptic plasticity is to maintain neural circuits functional by continuously adapting them, however, rules that consider aspects of neural activity beyond its mere presence or absence, may be useful. One such rule, which had been proposed a long time ago and turned out to be actually applied in the brain later on, will be introduced in the following section.

Hebb's conjecture

In 1949, Donald Hebb proposed that a connection between neurons a and b should be strengthened if neuron a repeatedly takes part in firing neuron b (see Figure 2.2A). Hebb's rule fulfills the requirement of locality: it takes into account only the activity of the two neurons. The important property of the rule is that it favors causal connections, i.e. it strengthens synapses that took part in firing the postsynaptic neuron. Thereby, Hebb's rule can account for associative learning. For example, the activity of neuron a and b might represent different percepts, such as tones of a melody, that always occur in the same sequence. Listening to that melody multiple times will cause neuron a to repeatedly fire before neuron b, such that their connection becomes stronger. The tone that causes neuron a to fire will hence also start to activate neuron b, even if the next tone, that would have activated neuron b, does not appear. The second tone becomes associated with the first.

Early theoretical models implemented Hebbian learning according to the principle 'what fires together, wires together'. In these models, synapses change based on correlation rather than causality. Hence, strictly speaking, they simplify Hebb's idea. So-called *correlation-based* learning rules (Gerstner and Kistler, 2002) do not require knowledge about the relative order of neuronal activity, and have been used in rate-based models (where neuronal firing rate instead of individual spikes is modeled). The simplest formulation of Hebbian learning in this sense is

$$\frac{\mathrm{d}w}{\mathrm{d}t} = \eta r_{pre} r_{post}, \tag{2.2}$$

where r_{pre} and r_{post} refer to the firing rates of pre- and postsynaptic neurons, and η is a positive constant. These models appeared before Hebb's conjecture was experimentally confirmed.

Spike-timing dependent plasticity

First experimental support for Hebb's idea came from experiments showing that neural activity can lead to a long-lasting increase in synaptic strength, termed *long-*

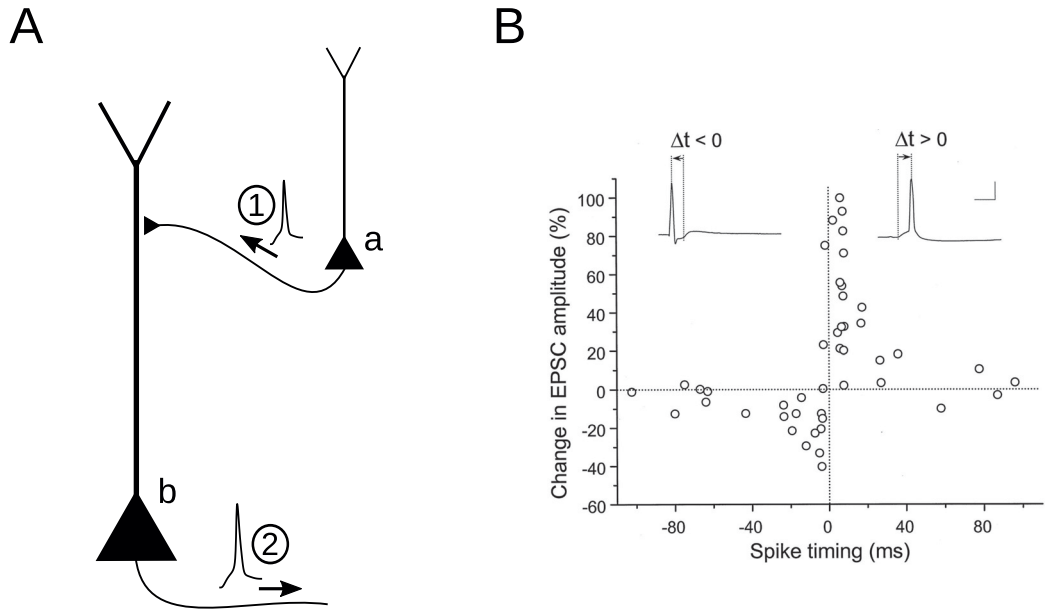

Figure 2.2: **Hebb's proposal and spike-timing dependent plasticity.** A. Illustration of two connected neurons that fire in a causal manner. Neuron a's axon terminates on neuron b's dendritic tree. A causal firing pattern is given, if neuron a fires an action potential (1) before neuron b fires an action potential (2). B. Spike-timing dependent plasticity. Taken with permission from Bi and Poo (1998). Two connected neurons in a culture were repeatedly stimulated to spike relative to each other with a particular timing. The change in synaptic strength (measured as the amplitude of the excitatory postsynaptic current (EPSC) is depicted as a function of the relative spike timing of the two connected neurons ($\Delta t = t_{post} - t_{pre}$). Potentiation occurred if the presynaptic neuron fired before the postsynaptic neuron ($\Delta t > 0$), and depression occurred for the reverse order ($\Delta t < 0$).

term potentiation (Bliss and Gardner-Medwin, 1973; Bliss and Lomo, 1973). A synaptic learning rule that closely resembles Hebb's proposal was later found, in the 1990s, when different labs discovered that the order in which two connected neurons spike can determine the sign of synaptic change: *spike-timing dependent plasticity*. As in Hebb's rule, pre- before postsynaptic activity resulted in increased synaptic strength, but additionally, the opposite order – post before pre – resulted in decreased synaptic strength (Bi and Poo, 1998; Debanne et al., 1998; Feldman, 2000; Markram, 1997; Zhang et al., 1998) (see Figure 2.2B). This classical form of spike-timing dependent plasticity (STDP) observed in excitatory principal cells – in contrast to simple correlation-based Hebbian plasticity – is thus bidirectional and asymmetric: both long-term potentiation (LTP) and depression (LTD) occur dependent on the relative spike timing.

$$\Delta w = \begin{cases} A_+ \exp(\frac{-\Delta t}{\tau_+}) & \text{if } \Delta t \geq 0 \\ -A_- \exp(\frac{\Delta t}{\tau_-}) & \text{if } \Delta t < 0 \end{cases} \tag{2.3}$$

where $\Delta w = \frac{\mathrm{d}w}{\mathrm{d}t}$ denotes the change in synaptic strength. The potentiation fac-

tor A_+ and the depression factor A_- determine the maximum amount of synaptic change, which decreases exponentially as a function of the difference between pre- and postsynaptic spike times: $\Delta t = t_{post} - t_{pre}$. The time course of the exponential decrease is determined by the time constants τ_+ and τ_- for potentiation and depression, respectively.

Theoretical studies demonstrated interesting computational consequences of STDP: The asymmetry favors unidirectional connections that are suitable for feedforward processing and storing sequences (Abbott and Blum, 1996; Blum and Abbott, 1996; Mehta et al., 1997; Rao and Sejnowski, 2000). STDP enables neural circuits to become selective to correlated inputs, because it strengthens synapses with a causal timing relation to the postsynaptic spike (Kempter et al., 1999; Song and Abbott, 2001; Song et al., 2000). Correlated synaptic activations yield larger postsynaptic depolarizations than activations of uncorrelated synapses. Hence, correlated synapses are more likely to cause postsynaptic firing and to potentiate because they activated before they caused a postsynaptic spike. Unlike Hebbian or correlation-based learning, STDP enforces competition between synapses by incorporating synaptic depression (van Rossum et al., 2000).

Mechanism underlying STDP

Synapses that undergo plasticity according to the relative timing of neural activity, such as STDP, need (i) to be informed about pre- and postsynaptic spiking, and (ii) a mechanism that transforms information about pre- and postsynaptic spike times into a synaptic change.

(i) At a synapse, presynaptic spiking is reflected in the amount of neurotransmitters released into the synaptic cleft. These neurotransmitters bind to receptors in the postsynaptic membrane. The direction of signaling from pre- to postsynaptic neurons naturally entails that the postsynaptic neuron is well informed about presynaptic activity – long-term forms of plasticity often depend on what happens postsynaptically. Postsynaptic spiking, however, also has to be signaled to the postsynaptic site of the synapse; most neurons have elaborate dendritic trees such that their synapses are far away and electrotonically separated from the spike initiation zone (the axonal region where action potentials are generated). However, action potentials do not only propagate actively down the axon, but also back into the dendrite (Spruston et al., 1995; Stuart et al., 1997a; Stuart and Sakmann, 1994). The latter so-called *backpropagating action potentials* (bAPs) can signal action potential firing to synapses in the dendritic tree (Magee and Johnston, 1997; Markram, 1997) (see also Figure 2.3A).

(ii) Non-Methyl-D-Aspartate receptors (NMDAR) in the postsynaptic membrane detect coincident pre-and postsynaptic activity; they permit calcium influx if both presynaptic glutamate binds to the receptor and a postsynaptic depolarization removes a magnesium block (Bi and Poo, 1998; Debanne et al., 1998; Magee and Johnston, 1997; Markram, 1997; Zhang et al., 1998, see also Figure 2.3B). This depolarization can be provided by bAPs. Depending on the amount of intracellular calcium, different intracellular pathways activate (Malenka and Siegelbaum, 2001). Thereby the amount of calcium can determine whether the synapse undergoes LTP or LTD. If additionally, the temporal order of pre- and postsynaptic factors influences the amount of calcium,

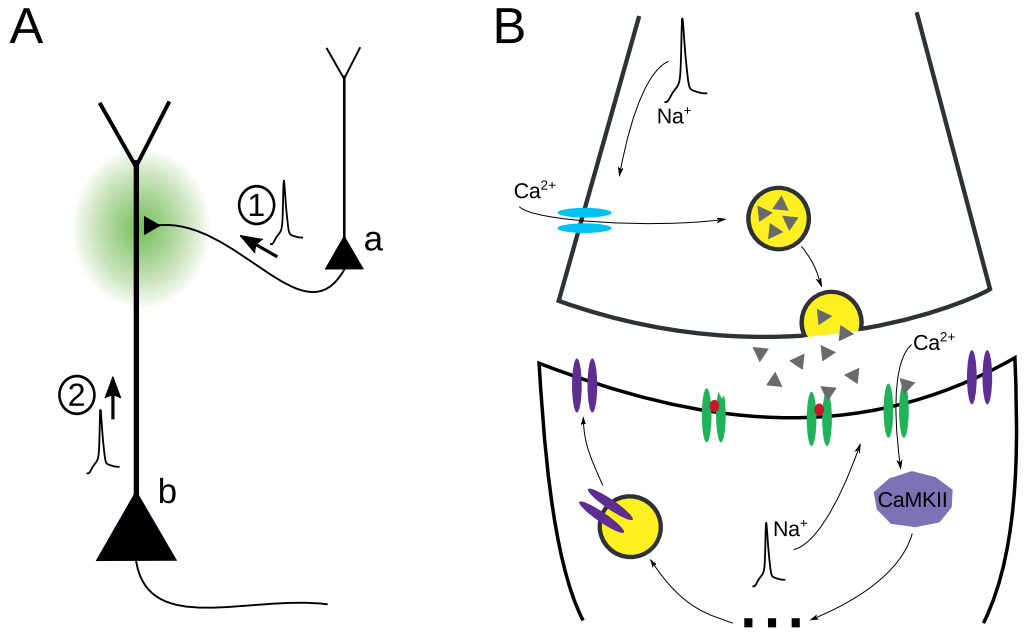

Figure 2.3: **Mechanism underlying STDP.** A. The synapse receives information about pre- and postsynaptic spike timing via the action potential of the presynaptic neuron and the bAP of the postsynaptic neuron, respectively. If the presynaptic action potential (1) arrives at the synapse before the bAP (2), LTP occurs at synapses undergoing classical STDP. B. Induction mechanism at the synapse. The presynaptic action potential depolarizes the presynaptic membrane, voltage-gated calcium channels open, calcium enters the cell and triggers a signaling cascade that leads to exocytosis of neurotransmitters (gray triangles) into the synaptic cleft. In the postsynaptic membrane, NMDA channels (green) are closed if the postsynaptic membrane is at the resting potential. Upon arrival of the bAP, the depolarization of the membrane releases the magnesium block (red) from NMDA channels, which still remain effectively closed, because they are ligand-gated. When neurotransmitters bind to the prepared NMDA channels, a large amount of calcium can enter the postsynaptic membrane and initiate a cascade of signals, including activation of Calcium-Calmodulin kinase II (CaMKII), that leads to LTP. On the one hand, the nucleus receives a signal for gene expression to produce new receptor proteins (purple) for the synapse. On the other hand, calcium can also activate kinases that phosphorylate postsynaptic receptors, increasing their conductance.

then – to get classical STDP – pre-before-post should cause large amounts of calcium that activate the LTP pathway, and post-before-pre should cause intermediate amounts of calcium that activate the LTD pathway. Indeed, the interplay between an excitatory postsynaptic potential (EPSP) caused by glutamate binding to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptors and a bAP can lead to different amounts of calcium entering through NMDARs: if the EPSP occurs before the bAP reaches the synapse, the EPSP can inactivate A-type potassium channels (Hoffman et al., 1997; Migliore et al., 1999) and thereby boost the bAP (Magee and Johnston, 1997). The resulting supralinear summation of EPSP and bAP causes an increased amount of calcium influx through NMDARs. The intracellular processes for LTP and LTD are thus sensitive to the temporal order of pre- and postsynaptic activity.

The importance of the backpropagating action potential for STDP

In the previous section, I introduced the backpropagating action potential, which informs synapses about postsynaptic action potential firing. It does so in a timely and accurate fashion as it actively propagates along the dendrite with high speed. Besides being a neat explanation for how STDP could be realized, experimental studies demonstrated the relevance of the bAP for learning; together they suggest that bAPs are essential for classical STDP: First, blocking backpropagation with the sodium channel blocker tetrodotoxin abolishes STDP (Magee and Johnston, 1997; Markram, 1997). Second, when bAPs coincide with EPSPs, calcium responses add supralinearly in CA1 (Magee and Johnston, 1997; Yuste and Denk, 1995) and layer 5 (Koester and Sakmann, 1998; Schiller et al., 1998) pyramidal neurons, which could explain why coincident activity leads to LTP. Finally, calcium responses are sensitive to the relative timing of pre- and postsynaptic spikes (Koester and Sakmann, 1998) – explaining the timing-dependence of plasticity. Taken together, the bAP likely plays a mechanistic role for STDP and its timing requirements.

Frequency dependence of synaptic plasticity

Soon after the discovery of STDP, it became clear that timing is only one factor that determines the magnitude and direction of synaptic change. For instance, synaptic plasticity additionally depends on the frequency of stimulation (Sjöström et al., 2001). While low-frequency stimulation depresses synapses, high-frequency stimulation potentiates them, regardless of spike timing; hence, bidirectional connections can form at high firing rates (Sadeh et al., 2015). Frequency-dependent plasticity may be explained according to the same principles underlying STDP: a high frequency train of bAPs causes a large calcium influx by itself, which could induce LTP regardless of the precise timing of the EPSP relative to individual bAPs. Alternatively, the train of bAPs could open a critical amount of voltage-gated calcium channels triggering a dendritic calcium spike (Sjöström et al., 2001); these strong and relatively long-lasting depolarizations can also trigger LTP (Golding et al., 2002). In the following section, we will discover that dendrites support various types of spikes with interesting consequences for synaptic plasticity.

Dendritic-spike mediated plasticity

With the advancement of experimental techniques for patching, recording, and imaging dendrites, many studies demonstrated that diverse action potentials mediated by sodium, calcium, or NMDA currents originate in dendrites *in vitro* and *in vivo*. Interestingly, single occurrences of these dendritic spikes can induce LTP (Gambino et al., 2014; Golding et al., 2002; Humeau and Lüthi, 2007) or LTD (Holthoff et al., 2004) in the absence of bAPs. Hence, this form of plasticity can be conceivably faster than STDP and allows for *single-shot* learning as it does not demand repeated pairings of pre- and postsynaptic activity. In contrast to STDP, dendritic-spike mediated synaptic plasticity requires spatially clustered inputs (Holthoff et al., 2004; Losonczy and Magee, 2006; Polsky et al., 2004), and depending on the spatial extension of the dendritic spike, may occur only locally; NMDA-spikes, for instance, do not propagate as they require

glutamate binding and hence induce plasticity only in confined parts of the dendritic tree (Schiller et al., 2000).

Diversity of plasticity rules

Given the information from the previous sections, it seems evident that synaptic strength changes based on characteristics of neural activity, such as timing or frequency. This enables us to learn the statistics of the environment based on incoming sensory information (experience). The exact rules governing synaptic plasticity, however, are not set in stone. Instead, where we measure matters (for a review see Caporale and Dan, 2008). Particularly, they differ between brain areas, cell types, and locations in the dendrite (Froemke et al., 2010, 2005; Letzkus et al., 2006; Sjöström and Häusser, 2006). Presupposing that different brain areas, cell types, and dendritic areas fulfill different functions, this strongly suggests that synaptic plasticity is adjusted to functionality.

2.2 Modulation of synaptic plasticity

So far, I have introduced activity-dependent rules for synaptic plasticity, where the synaptic change was solely dependent on the spiking activity of the connected neurons. In the beginning, I mentioned that synapses change due to local biochemical processes, which are dependent on local factors such as the current strength of the synapse. From the perspective of the synapse, there might be a single recipe for synaptic change based on many factors. However, from the perspective of the experimenter, it is only possible to change one variable at a time to obtain a controlled measurement. As a result, a change in the dependent variable, like the synaptic strength, is measured as a function of only one independent variable, like the difference in timing of the spikes in the two connected neurons. This method cannot immediately capture the complexity of the molecular machinery that takes a myriad of factors (among which spike timing is only one) into account to determine synaptic change. Therefore, the portrayal of synaptic plasticity as a function of spike-time differences is inaccurate, but when combined with other measurements, it might provide a decent first approximation. In the following, I refer to the simplified definition of synaptic plasticity as a function of the difference in spike times as the *plasticity rule* and consider all other factors that influence the shape of this rule as modulators of that rule. This terminology is common, which may have historical reasons, and it additionally highlights the role of neural spiking activity, which is associated with sensory stimuli. In the following, I describe different kinds of plasticity(-rule) modulation.

2.2.1 Plasticity of Plasticity

Synaptic plasticity rules are themselves plastic, i.e. whether and how synapses change is subject to factors other than the current activity of the connected neurons at the time of induction.

First, synaptic change depends on synaptic strength and average neural activity. At generally low activity levels, synaptic strengths rise more easily, while at high activity levels, they drop more easily (Lissin et al., 1998; Turrigiano et al., 1998), referred to as

synaptic scaling. Theoretical models incorporated such *homeostatic plasticity* long before it was experimentally measured: synaptic scaling is part of Oja's rule (Oja, 1982), where synaptic strength decreases proportional to the square of the postsynaptic firing rate. A similar concept, an activity-dependent sliding threshold, can be encountered in the Bienenstock-Cooper-Munro model (Bienenstock et al., 1982), where the threshold for plasticity increases with firing rate.

Second, synaptic activity and change in synaptic strength can prime plasticity induction, i.e. it can determine how easily *subsequent* plasticity can arise, also referred to as *metaplasticity*. Such altered plasticity thresholds, on the order of a few hours, occur on the behavioral level, during development (Kirkwood et al., 1996) or learning (Cohen-Matsliah et al., 2007; Moyer et al., 1996; Oh et al., 2003) and after environmental enrichment or stress (Kim et al., 1996), and on the cellular level, after activation of synaptic receptors (Christie and Abraham, 1992; Cohen and Abraham, 1996; Huang et al., 1992).

Both homeostatic plasticity and metaplasticity can stabilize learning: they keep the total amount of activity moderate, e.g. by downscaling all synapses of a neuron equally depending on the activity of the neuron – in contrast to other mechanisms (such as STDP) that change individual synapses based on the synapses' unique contribution. Additionally, homeostatic mechanisms could regularize learning. By limiting repeated adjustments of the same synapses, they could prevent overfitting to the presented stimuli, and hence facilitate generalization to new but similar stimuli.

2.2.2 Neuromodulation and disinhibition

In contrast to homeostatic plasticity and metaplasticity, neuromodulation can *globally* change plasticity *at the time of induction* based on context or the state of the organism. Although ultimately local factors at the synapse are modulated, neuromodulation deserves to be called modulation, because it exerts powerful top-down control over plasticity. Unlike local processes that gradually adjust plasticity rules, neuromodulation can have sudden switch-like effects on plasticity. We will see in the following that the switch-like character is mediated by inhibition and disinhibition, which play important roles during neuromodulation of learning.

Inhibition is one factor that has been linked to plasticity on a number of levels. First, critical period plasticity (temporally enhanced plasticity during early lifetime) ends when inhibitory neurons mature. Second, while increased inhibition interferes with learning (Arolfo and Brioni, 1991; Davis, 1979; Harris and Westbrook, 1995; McNaughton and Morris, 1987; Sanger and Joly, 1985), decreased inhibition facilitates learning (Brioni et al., 1989; Izquierdo et al., 1993). Finally, disinhibition, the inhibition of inhibition, promotes learning in fear conditioning paradigms (Letzkus et al., 2011; Wolff et al., 2014). All this supports the idea that inhibition is the default condition in adults and that active disinhibition opens the essential windows for learning (Young, 1964). Neuromodulators such as dopamine, acetylcholine, serotonin, or oxytocin are well suited to orchestrate these windows for learning: they target disinhibitory circuits (Froemke et al., 2007; Letzkus et al., 2011) and they signal diverse behaviorally relevant conditions such as reward, surprise, novelty, social context, mood, and fear. Importantly, disinhibition manifests during a wide range of behaviors such as whisking

(Gentet et al., 2012; Lee et al., 2013, glutamatergic from higher areas), locomotion (Fu et al., 2014), social behaviors (Marlin et al., 2015; Owen et al., 2013), and attention (Zhang et al., 2014, glutamatergic from higher areas). Taken together, neuromodulation and disinhibition play a role during learning and seem to be behaviorally relevant.

2.3 Disinhibitory circuits

With the importance of inhibition and disinhibition laid out in the previous sections, I now turn to an in-depth discussion of disinhibitory circuits, which could mediate those mechanisms for plasticity control that we focus on in this thesis.

Neuromodulatory pathways provide disinhibition to principal neurons in disinhibitory circuits (Froemke et al., 2007; Letzkus et al., 2011), which have been identified in various cortical areas (Dávid et al., 2007; Lee et al., 2013; Pfeffer et al., 2013; Pi et al., 2013). In these circuits, layer 1 interneurons (often expressing vasoactive intestinal peptide: VIP) have been observed to inhibit other interneurons that target pyramidal neurons. The neuromodulatory activation of layer 1 interneurons removes inhibition from pyramidal neurons. In the following, I introduce the major players in disinhibitory circuits, pyramidal neurons and interneurons, as well as typical circuit motifs.

2.3.1 Pyramidal neurons

Pyramidal neurons constitute the most common type of excitatory projection neuron; they can be found in all areas of the cerebral cortex, the hippocampus, and the amygdala (Ramon y Cajal, 1995). Next to being considered the primary information processing units, most synaptic plasticity experiments were conducted in these neurons, and they are the targets of disinhibition during learning. In this thesis, we focus on pyramidal neurons found in cortical layer 5 (L5) and hippocampal CA1, which share characteristics that make them likely candidates for dendritic plasticity modulation:

(i) Compartmentalized excitatory inputs: Both, L5 and CA1 pyramidal cells extend over multiple layers, and hence receive inputs from different pathways onto different areas of their dendritic trees (Spruston, 2008). Local inputs tend to arrive close to the soma on basal and proximal apical dendrites, and inputs from other areas typically impinge onto distal apical dendrites: L5 pyramidal neurons receive excitatory inputs from the local-circuit (proximal) as well as from other cortical areas and from non-specific thalamic nuclei (distal) (Larkum, 2013; Spruston, 2008). In CA1 pyramidal neurons, Schaffer collateral synapses from CA3 are found on the proximal dendrite while thalamic inputs and perforant path synapses from the entorhinal cortex arrive more distally (Amaral and Lavenex, 2007).

(ii) Active dendritic signaling: bAPs attenuate similarly in L5 and CA1 pyramids (Stuart et al., 1997b) and both neuron types have an additional dendritic calcium spiking zone that is believed to couple proximal and distal inputs (Larkum et al., 1999b). Distal excitatory input that is coincident with a backpropagating action potential leads to a calcium spike in the apical tuft that causes the neuron to burst. This highly nonlinear response seems to detect coincident proximal and distal inputs, because single bAPs or moderate distal input alone cannot trigger it. This phenomenon, termed BAC-firing in

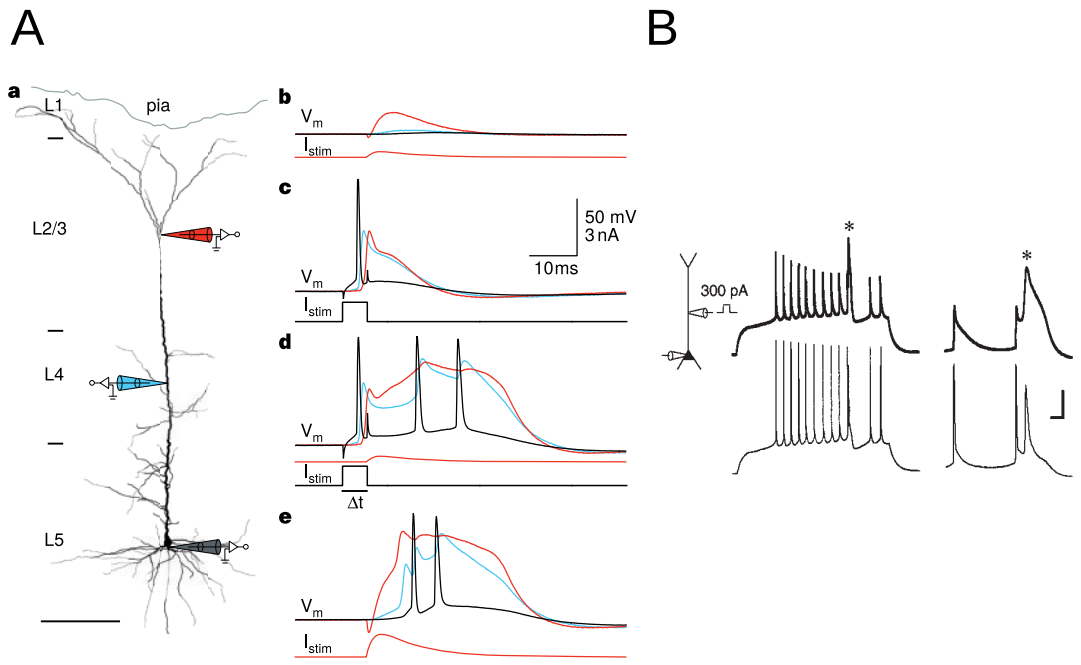

Figure 2.4: **Calcium-spike induced burst firing.** A. BAC firing. a) L5 pyramidal neuron with three stimulation/recording sites. b) Distal stimulation alone leads to an EPSP in the dendrite, but no significant somatic depolarisation. c) Somatic current injection causes an action potential that propagates back into the dendrite. d) Coincident dendritic and somatic current injection triggers a dendritic calcium spike that drives the soma to fire a burst of action potentials, the BAC firing mode. e) Strong dendritic current injection can also elicit calcium spikes that cause a burst of action potentials. Taken with permission from Larkum et al. (1999b). B. Dendritic stimulation of a CA1 pyramidal neuron causes a calcium spike in the dendrite that drives a burst in the soma. Taken with permission from Golding et al. (1999).

L5 pyramidal neurons (Larkum et al., 1999b, Figure 2.4A), occurs in a similar fashion in CA1 pyramidal neurons (Golding et al., 1999, Figure 2.4B).

(iii) Compartmentalized inhibitory inputs: Both pyramidal neuron types are highly innervated by a diverse set of inhibitory interneurons that impinge onto distinct parts of the dendritic tree (Kullmann and Lamsa, 2011; Markram et al., 2004). The compartmentalization of inhibitory inputs into proximal and distal dendritic areas compares to that of excitatory inputs. The sheer amount and diversity of interneuron inputs suggests that they function as modulators of spiking output and dendritic processing of pyramidal neurons.

2.3.2 Common circuit motifs

Pyramidal neurons, in general, are embedded in complex local circuits. Common inhibitory circuit motifs provide feedforward and feedback inhibition to the pyramidal neurons (see Figure 2.5). In feedforward circuits, principal neurons are innervated by interneurons that receive a common excitatory input (Figure 2.5A). In feedback circuits, the interneurons are activated by the principal neuron itself (recurrent, Figure

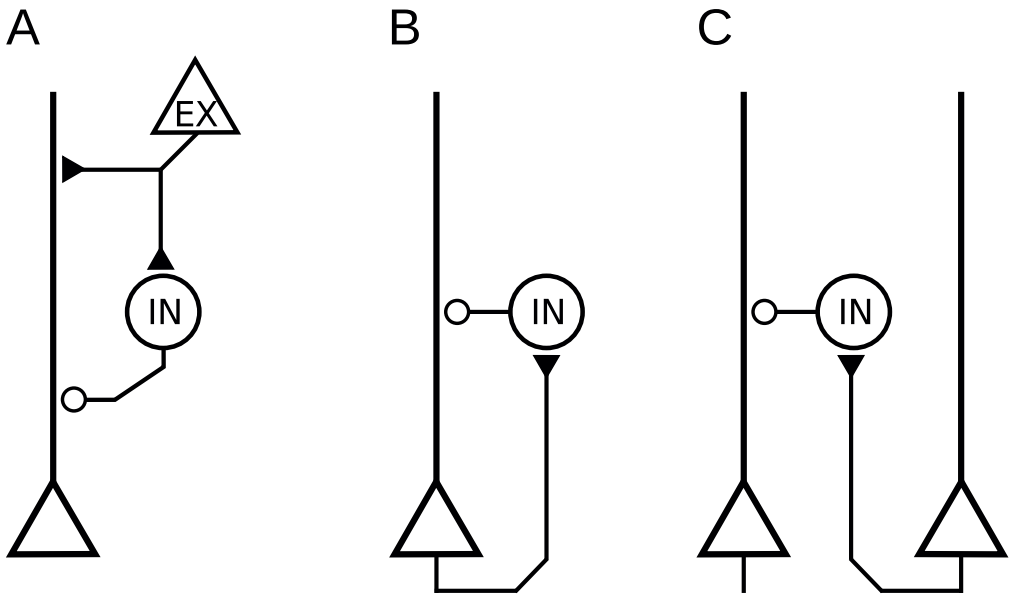

Figure 2.5: **Common circuit motifs.** A. Feedforward inhibition. Pyramidal neuron and interneuron (IN), receive the same excitatory drive (EX). B. Recurrent feedback inhibition. The pyramidal neuron excites an interneuron (IN) that in turn inhibits the pyramidal neuron. C. Lateral feedback inhibition. A pyramidal neuron receives feedback inhibition that is stimulated by another pyramidal neuron.

2.5B), or by another principal neuron in the same hierarchy (lateral, Figure 2.5C). In both feedforward and feedback circuits, inhibition tends to arrive with a delay to the excitatory input. The minimum delay possible is larger in feedback circuits, because principal neurons have to fire to recruit inhibition. Disinhibitory circuits are (feedforward or feedback) inhibitory circuits that are themselves under inhibitory control. In these circuits, inhibitory neurons disinhibit principal neurons by silencing those interneurons that target principal neurons.

2.3.3 Interneurons

Interneurons form local connections, occur in all cortical layers, and are very heterogeneous with regard to their connectivity, morphology, electrophysiology, synaptic properties, and genetic markers (Kullmann and Lamsa, 2011; Markram et al., 2004, Figure 2.6). Several attempts have been made to classify cortical (including hippocampal) interneurons. A very general classification can be made based upon their targets: perisomatic versus dendritic regions of principal neurons, or other interneurons (interneuron-specific interneurons, Acsády et al., 1996; Gulyás et al., 1996; Hájos et al., 1996). Neocortical interneurons have also been broadly classified into three major groups based on whether they express parvalbumin (PV), somatostatin (SOM) or the ionotropic serotonin receptor 5HT3a (Rudy et al., 2011). The latter group includes vasointestinal peptide (VIP)-expressing interneurons. Specimen from all three groups

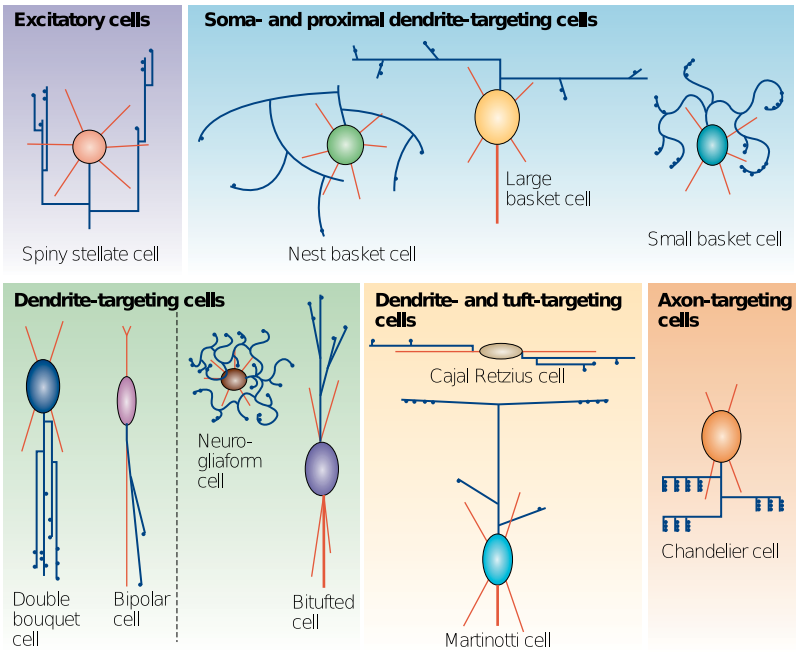

Figure 2.6: **Diversity of neocortical interneuron types.** Taken with permission from Markram et al. (2004)

play relevant roles in the disinhibitory circuits regarded here by fulfilling distinct functions: PV cells inhibit proximal dendritic and somatic regions of pyramidal neurons (Rudy et al., 2011), and typically provide feedforward inhibition (Cruikshank et al., 2007; Gabernet et al., 2005; Pouille and Scanziani, 2001). SOM cells target the apical and basal dendrites of pyramidal neurons (Rudy et al., 2011) and can provide both feedforward and feedback inhibition (Kapfer et al., 2007; Silberberg and Markram, 2007; Tan et al., 2008). VIP cells target PV and SOM interneurons (Dávid et al., 2007; Pfeffer et al., 2013) and can hence control inhibitory circuit activation and principal neuron disinhibition. Although differences in the particular subtypes of interneurons exist between cortical areas and the hippocampus, interneuronal circuits are similar in that they target specific dendritic regions, express PV, SOM, and VIP, and form feedforward, feedback, and disinhibitory motifs (Kullmann and Lamsa, 2011; Vida, 2010).

2.4 A cellular mechanism for controling plasticity

In the previous sections I have motivated that (dis-)inhibition of principal neurons is important during learning. Whereas there are many studies supporting this observation, the exact cellular processes explaining the effects of disinhibition on learning still remain to be understood. In principle, inhibition could influence synaptic plasticity indirectly by reducing neuronal firing rate. However, given that dendritic spikes can induce plasticity in the absence of neuronal firing, another, more direct way seems more practical: inhibition could target dendritic signals required for inducing plasticity, such as bAPs (Markram, 1997; Paulsen and Moser, 1998) or calcium spikes (Golding

et al., 2002).

Supporting this view, several experiments have shown that dendritic inhibition can profoundly affect active dendritic signaling. First, inhibition limits the backpropagation of action potentials into the dendrite (Buzsáki et al., 1996; Miles et al., 1996; Tsubokawa and Ross, 1996). Even single inhibitory synapses can significantly reduce the bAP at a high spatial and temporal resolution (Müllner et al., 2015). Second, single inhibitory interneurons can inhibit calcium spikes (Larkum et al., 1999b). A recent experimental study by Cichon and Gan (2015) shows that motor learning tasks induce dendritic calcium spikes that lead to synaptic changes and that the incidence of such events is greatly enhanced when SOM interneurons are inhibited. By targeting single spines and NMDA spikes, inhibition can influence synaptic plasticity on a local scale (Higley, 2014). Taken together, dendritic inhibition likely operates as a powerful direct modulator of different types of synaptic plasticity.

3 Aims and main questions of this thesis

The aim of this thesis is to contribute to the understanding of how inhibition controls plasticity processes on a single cell level. I now further specify this goal by stating the main research questions addressed in the subsequent chapters.

In the previous chapter, I presented experimental support for a role of disinhibitory circuits during learning. By providing a switch for pyramidal neuron dendritic inhibition, these circuits likely exert control over intracellular plasticity processes. The involved inhibitory neurons are well suited – due to their position on the dendrite – to target bAPs (proximal inhibition) and calcium spikes (distal inhibition). Here, we focus on the modulation of these two signals, which have high computational potential because (i) they can act globally, in comparison to e.g. NMDA spikes, such that their control can have an extensive impact on plasticity (ii) together they can cover the whole dendritic tree, allowing for all-encompassing control, and (iii) they arise from and couple the two main spiking zones of the neuron, suggesting that their modulation has implications for neural information processing beyond plasticity control.

While it has been shown that inhibition can eliminate bAPs and calcium spikes, the requirements for the strength and timing of inhibition remain to be explored in more detail. This leads us to the main questions studied in this thesis:

1. In the case of successful inhibition of the bAP, which occurs on the main shaft of the apical dendrite, can forward information flow be preserved? Given that different interneurons could be modulated independently from each other, how does inhibition in one region of the dendrite interact with dendritic signals in other regions? In other words, is it possible to modulate the dendritic signals in isolation? These questions will be tackled in the first part of this thesis (Wilmes, Sprekeler, Schreiber 2016).

2. Given that inhibition of plasticity might be the default in adult brains, how can a robust modulation of dendritic signals for plasticity - i.e. without limiting information processing - be established in inhibitory circuits? We will address this question in the second part of this thesis (Wilmes, Schleimer, Schreiber 2016).

By investigating these questions we aim to contribute to a better understanding of the cellular processes involved in regulating plasticity. Due to the cellular nature of plasticity processes, we adopt the perspective of single cells in a microcircuit. To understand the interactions between inhibitory synapses and dendritic processes important for synaptic plasticity, we need to particularly focus on the dendrites of principal neurons that receive excitatory and inhibitory synapses from the microcircuit they are embedded in. Recording from dendrites at multiple locations is still experimentally challenging. Hence, computational modeling is a valuable first approach providing

experimentally testable predictions. We take this approach by adopting conductance-based multi-compartmental models of neurons. First, conductance-based models (as described in Koch, 1998) are based on detailed biophysical knowledge about neuronal membranes and their rich repertoire of ion channels. They provide a decent description of neurons and capture their main functional properties. Second, multi-compartmental models are well suited to capture the properties of spatially extended, and functionally compartmentalized dendrites. In particular, the signals we study here extend over multiple, but partially distinct compartments of the dendritic tree such that understanding their interactions requires multi-compartmental models. While anatomically detailed models exist and are also used in this thesis, we mostly study simplified morphologies. Next to computational efficiency, advantages of simple models with a limited amount of parameters are that they are easier to analyze and understand, and that results generalize better. For synaptic plasticity, we rely on phenomenological models, instead of biophysical models, because the biophysical mechanisms underlying STDP, and especially inhibitory STDP, are not yet fully understood. In particular, when we take the top-down approach, i.e. we derive an STDP rule from the function of the synapse, we start from an abstract model detached from the underlying biophysical mechanisms.

4 Inhibition as a binary switch for excitatory plasticity in pyramidal neurons

The following is a preprint of the paper published in Plos Computational Biology on March 22, 2016. The paper is typeset in the layout of the remaining thesis to ensure good readability of the content.

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☯ These authors contributed equally to this work.

Inhibition as a binary switch for excitatory plasticity in pyramidal neurons

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Abstract

Synaptic plasticity is thought to induce memory traces in the brain that are the foundation of learning. To ensure the stability of of these traces in the presence of further learning, however, a regulation of plasticity appears beneficial. Here, we take up the recent suggestion that dendritic inhibition can switch plasticity of excitatory synapses on and off by gating backpropagating action potentials (bAPs) and calcium spikes, i.e., by gating the coincidence signals required for Hebbian forms of plasticity. We analyze temporal and spatial constraints of such a gating and investigate whether it is possible to suppress bAPs without a simultaneous annihilation of the forward-directed information flow via excitatory postsynaptic potentials (EPSPs). In a computational analysis of conductance-based multi-compartmental models, we demonstrate that a robust control of bAPs and calcium spikes is possible in an all-or-none manner, enabling a binary switch of coincidence signals and plasticity. The position of inhibitory synapses on the dendritic tree determines the spatial extent of the effect and allows a pathway-specific regulation of plasticity. With appropriate timing, EPSPs can still trigger somatic action potentials although backpropagating signals are abolished. An annihilation of bAPs requires precisely timed inhibition, while the timing constraints are less stringent for distal calcium spikes. We further show that a wide-spread motif of local circuits – feedforward inhibition – is well suited to provide the temporal precision needed for the control of bAPs. Altogether, our model provides experimentally testable predictions and demonstrates that the inhibitory switch of plasticity can be a robust and attractive mechanism, hence assigning an additional function to the inhibitory elements of neuronal microcircuits beyond modulation of excitability.

Author Summary

We must constantly learn in order to meet the demands of a dynamically changing environment. The basis of learning is believed to be synaptic plasticity, i.e. the potential of neuronal connections to change. Depending on context, however, it may be either useful to learn and modify connections or, alternatively, to keep an established network structure stable to maintain what has already been learned (also referred to as the plasticity-stability dilemma). The ability to switch synaptic plasticity on and off in a

flexible way hence constitutes an attractive feature of neuronal processing. Here, we analyze a cellular mechanism based on the inhibition-mediated gating of coincidence signals required for Hebbian forms of excitatory synaptic plasticity. While experimental evidence in support of individual steps involved in this mechanism is accumulating, it is as of now unclear whether this mechanism can indeed operate robustly under physiologically realistic parameters of pyramidal cells, in particular, without impairing information flow in these cells altogether. Computational modeling allows us to demonstrate that this is indeed possible if inhibition is well timed (on the order of 1 ms). Moreover, we show that a specific design of the local circuit can ensure the necessary timing.

4.1 Introduction

To successfully interact with our environment, we need to adjust to new or changing conditions. It is widely accepted that this ability involves alterations of synaptic connections in the brain, so-called synaptic plasticity (Martin et al., 2000). While synaptic plasticity fulfills key requirements for the incorporation of new knowledge and memories into neural circuits, it also introduces the risk of changing connections that are essential for previously stored information, a problem termed plasticity-stability dilemma (Abraham and Robins, 2005; Fusi et al., 2005). Hence, a mechanism to selectively switch plasticity on or off would be useful.

In this context, inhibition has been proposed as a means to regulate plasticity (Häusser and Mel, 2003; Paulsen and Moser, 1998; Tsubokawa and Ross, 1996). GABAergic interneurons that target the dendrites of pyramidal cells may control backpropagation of action potentials to excitatory synapses and hence the coincidence signal required for Hebbian forms of synaptic plasticity. Alternatively, such inhibition could affect the NMDA-receptor-mediated component of excitatory postsynaptic potentials (EPSPs) (Bar-Ilan et al., 2012; Paulsen and Moser, 1998). Indeed, recent experimental work has shown that inhibitory dendritic synapses can weaken the backpropagating action potential (bAP) in the dendrite of pyramidal cells so that calcium signals required for the plasticity of excitatory synapses are reduced (Müllner et al., 2015). These findings provide strong support for a crucial role of inhibition as a regulator of plasticity, in particular as direct stimulation of inhibitory neurons leads to a cancelation of bAPs in pyramidal cells. For an effective switch in plasticity, however, it needs to be ensured that while the dendritic inhibition cancels the bAP, the forward-directed EPSP (that is meant to cause the bAP in the first place) still reaches the soma and orthodromic information flow is preserved. Whether a separation of the effect of inhibition on EPSP and bAP is possible on physiological time scales is currently unclear and needs to be explored in view of the well-known efficiency of 'on-path' inhibition in impairing passive EPSPs in the dendrite (Koch et al., 1983). We here address this question as well as identify the temporal and spatial constraints that are required to reliably modulate plasticity of excitatory synapses in pyramidal cells.

To this end, mathematical modeling suggests itself, because it allows to systematically vary both the strength and dendritic location of inhibition and to monitor bAPs and calcium spikes in the whole dendrite with high temporal and spatial resolution. We hence adapted a multi-compartmental model of pyramidal cells to reproduce a number

of key electrophysiological characteristics. These included a realistic decrease of the amplitude of bAPs along the dendritic tree (Spruston et al., 1995), characteristics of bAP-activated calcium spike (BAC) firing (Larkum et al., 1999b), and the generation of distal calcium spikes at a critical frequency of somatic stimulation (Larkum et al., 1999a). Using this model, we identify conditions under which a modulation of bAPs and calcium spikes is possible and does not impair the forward-directed information flow to the soma.

We demonstrate that shunting inhibition gates bAPs and calcium spikes in an all-or-none manner, laying the foundation for a binary switch of plasticity of excitatory synapses. Further, we identify the timing constraints for an efficient inhibitory gating of bAPs and calcium spikes. Implementing an additive spike-timing dependent plasticity (STDP) rule (Song et al., 2000), we find that plasticity of excitatory synapses is indeed switched as a consequence of the effects of inhibition on the coincidence signal. Depending on the site of inhibition, this effect can be more global or constrained to smaller dendritic compartments and hence also distinct pathways converging onto pyramidal neurons. We observe that timing constraints for the gating of bAPs are relatively strict in that inhibition has to arrive with a precision of ~1 ms. Local gating of distal calcium spikes, however, can be achieved within a wider time window of several milliseconds. Additionally, calcium spikes are more sensitive to inhibition in that smaller conductances suffice to abolish them. Importantly, with appropriate timing of inhibition, forward-directed EPSPs can still drive somatic firing while Hebbian coincidence signals are canceled. Finally, we suggest that a common circuit motif of feedforward inhibition can ensure the appropriate timing required for the plasticity switch by inhibition. Our model study provides testable experimental predictions and strengthens the view that the functional role of interneurons includes a pathway-specific regulation of plasticity, in addition to the widely studied regulation of excitability and information flow in local networks (Isaacson and Scanziani, 2011).

4.2 Results

Pyramidal cells form one of the most important classes of projection neurons in the mammalian brain. Their apical and basal dendrites often receive synaptic inputs that originate from different pathways (Spruston, 2008). Accordingly, these cells are an appealing target for pathway-specific computations. Here, we focus on cortical layer 5 and hippocampal CA1 pyramidal neurons. Besides extending over multiple layers, these neuron types share physiological properties (Spruston, 2008) such as attenuating bAPs (Stuart et al., 1997b) and the generation of calcium spikes in the apical tuft (see e.g. Golding et al., 1999; Schiller et al., 1997). Hebbian plasticity of excitatory synapses in these cells is assumed to require a coincidence signal that provides information about the occurrence of somatic spikes to dendritic synapses. The hypothesis central to our study is that well timed and localized inhibition can selectively cancel bAPs or calcium spikes and hence impair synaptic plasticity at excitatory synapses further down the dendritic tree because of the missing coincidence signal.

We investigated the feasibility of such inhibition-mediated control of plasticity in a multi-compartmental model neuron with a simplified morphology capturing basic features of the dendritic compartments (including apical, oblique, and basal dendrites),

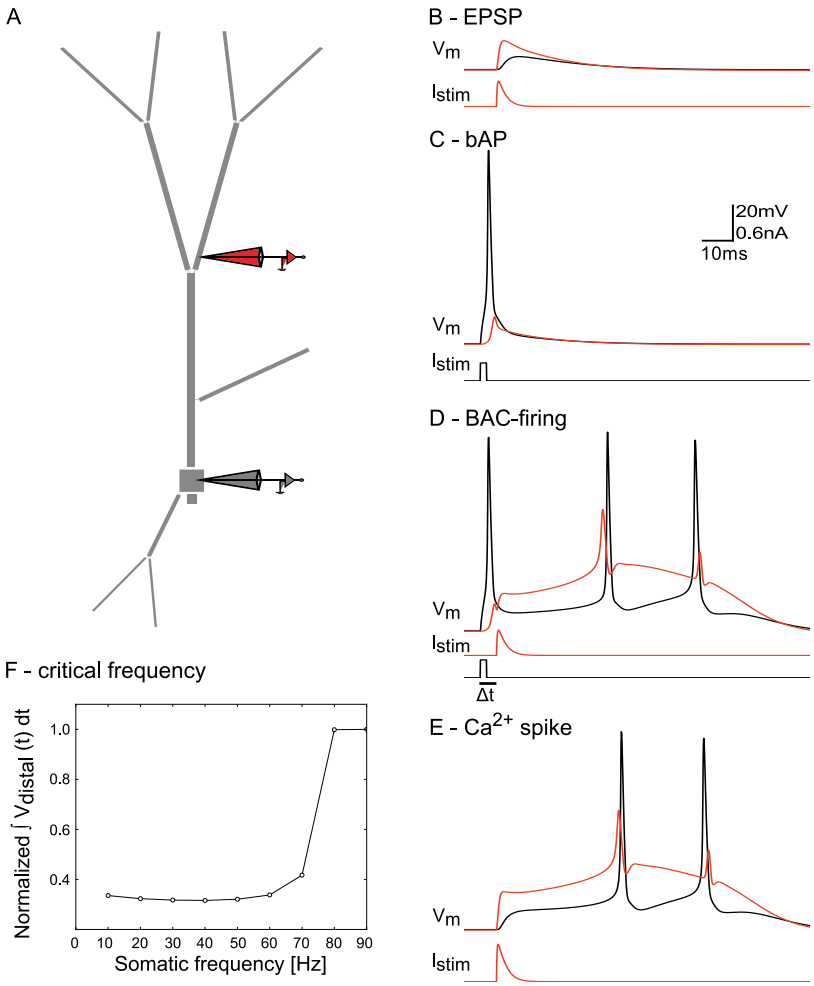


Figure 4.1: **Response properties of simplified pyramidal neuron model.** The model reproduces qualitative features of pyramidal neuron dendrites found in experiments by (Larkum et al., 1999b) and (Larkum et al., 1999a). The color of the voltage traces match the electrodes in the diagram. Scale bar applies to panels B-E. A: Model neuron morphology with somatic (black) and dendritic (red) recording and stimulation sites. B: EPSP: a distal EPSC (I_{stim}) resulted in an EPSP in the dendrite with little effect on somatic voltage. C: bAP: threshold somatic current injection (0.3 nA, 2 ms) led to a bAP. D: BAC firing: somatic current injection followed by dendritic stimulation in an interval (Δt) of 5 ms, resulted in a calcium spike, and a burst of two somatic APs. E: Calcium spike: stronger dendritic stimulation alone could elicit a calcium spike. F: Above a critical frequency of somatic spiking, a calcium spike was triggered. The y-axis depicts the cumulative membrane potential across the fixed simulation length of 0.6 sec for different frequencies of somatic stimulation. All values are normalized by the value at 90 Hz stimulation frequency (where a stereotypical calcium spike was elicited). The distal membrane potential changed abruptly once the frequency was high enough to trigger the calcium-dependent dendritic nonlinearity (i.e. the calcium spike).

as well as the soma and the axon (see Fig. 4.1A). Electrophysiological and biophysical parameters were chosen in physiologically realistic ranges and carefully adjusted to exhibit well-known properties of pyramidal cells. The model neuron captured a

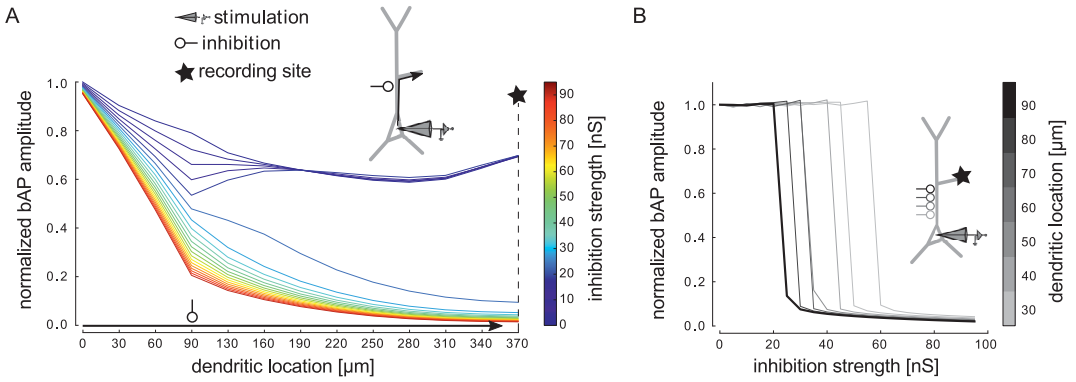


Figure 4.2: **Analysis of the effect of inhibition on the backpropagating action potential (bAP) in dependence on inhibitory conductance and dendritic location.** The bAP was triggered by threshold somatic current injection (as in Fig. 4.1C). A: Amplitude of the bAP on its path from the soma, along the proximal apical dendrite into the distal oblique dendrite (arrow), normalized to its amplitude at the soma, for different values of inhibition strength (lines in different colors). Inhibition with a double exponential time course (τ_{rise} = 0.5 ms, τ_{decay} = 5 ms) was placed on the proximal apical dendrite (90 µm from the soma). Inhibition onset was 2 ms after stimulation onset. The somatic spike peaked around 2.5 ms after stimulation onset. B: Amplitude of the inhibited bAP relative to the non-inhibited bAP as a function of inhibition strength, measured in the distal part of the oblique dendrite (indicated by the star in illustration and in A) for different locations of inhibition on the apical trunk (different shades indicate distance to soma in µm, thick line for 90 µm). Inhibition had an all-or-none effect on the bAP.

realistic decrease of the amplitude of bAPs along the dendritic tree (Spruston et al., 1995), characteristics of BAC firing (Larkum et al., 1999b), as well as the generation of distal calcium spikes at a critical frequency of somatic stimulation (Larkum et al., 1999a). Specifically, the neuron generated attenuating bAPs (Fig.4.1C) upon somatic current injection, and calcium spikes in the presence of coincident synaptic input in the distal part of the apical trunk (Fig. 4.1D), while distal input alone did not suffice to trigger a calcium spike (Fig. 4.1B). Calcium spikes in turn gave rise to a burst of two somatic action potentials. Such bursts have been observed in pyramidal neurons in hippocampal CA1 (Golding et al., 1999; Magee and Carruth, 1999), and cortical layer 5 (BAC firing, (Larkum et al., 1999b)). Hence, dendritic input modulated the gain of the somatic f-I curve. When stimulated to fire with increasing frequency, the model neuron produced a dendritic nonlinearity at a critical frequency of 80 Hz (Fig. 4.1F).

Inhibition was assumed to be shunting with rise and decay time constants of 0.5 ms and 5 ms, respectively. This kind of inhibition is commonly observed in pyramidal neurons receiving inhibitory $GABA_A$ synapses (Turner, 1990) and it acts locally (Koch et al., 1990; Rall, 1967). Finally, we also demonstrate that our main results generalize to an anatomically reconstructed and physiologically detailed L5 neuron model (Hay et al., 2011).

4.2.1 All-or-none modulation of backpropagating action potentials by inhibition

First, we sought to understand the effect of local dendritic inhibition on bAPs. To this end, we placed a shunting inhibitory input on the proximal apical dendrite, systematically varied its strength, and monitored the amplitude of a somatically-induced bAP along the apical dendrite. For weak inhibition, the bAP amplitude was reduced around the dendritic location of the inhibitory input, but recovered to its full amplitude as the bAP propagated down the dendrite. In contrast, strong inhibition barred the bAP from invading the dendrite (Fig. 4.2A). The transition from a fully intact bAP to a complete bAP failure occurred abruptly at a critical inhibitory conductance (Fig. 4.2B). This all-or-none behavior was observed for inhibition at different locations along the shaft of the apical dendrite, albeit with different critical amounts of inhibition (Fig. 4.2B). From the perspective of a synapse further up in the dendrite, the bAP was either fully intact or completely canceled. Fig. 4.2 shows the case for a synapse on the oblique dendrite, which is taken as a representative for one excitatory pathway subject to bAP-dependent STDP throughout the paper. The same effect could, however, also be observed for propagation into the apical tuft. The amount of inhibition required to cancel a bAP appeared to be in a realistic range. For example, when inhibition was placed at 90 µm from the soma (Fig. 4.2A and B), the critical inhibitory conductance was slightly above 25 nS, corresponding to ~25 co-activated inhibitory synapses of 1 nS (Pfeffer et al., 2013). Such inhibition could be provided by about 2-3 co-activated interneurons, given that interneurons form up to a dozen contacts onto a single pyramidal cell (Markram et al., 2004). We checked that the core observations of the effects of inhibition onto bAPs were not altered when shunting synaptic inputs were distributed along the dendrite (S1 Fig).

A moderate temporal jitter (on the order of 1 ms) in the activation of inhibitory synapses also did not abolish the all-or-none behavior, but when a critical amount of inhibition was reached too early, the neuron was prevented from spiking. Overall, however, timing of inhibition needed to be relatively precise, as we will outline in the following section, where we first present data on the compartment-specificity of the effects.

4.2.2 Compartment-specific inhibition

Due to its relatively local effect, shunting inhibition can control dendritic signals in a manner that is distinct between compartments, such as basal and apical dendrites. We hence investigated the effect of inhibition in different compartments (i.e. the basal, oblique, and distal apical dendrites, as well as the soma/axon), on the bAPs and calcium spikes, in the same and other compartments.

Modulation of bAPs

First, we consider the general case of bAP modulation in the absence of BAC firing. A systematic illustration of the effects of shunting inhibition on bAPs in different compartments is presented in Fig. 4.3A. We placed the inhibitory input in different locations and recorded the membrane potential dynamics throughout the dendrite to detect bAPs. Each panel shows the local membrane potential as a function of time in the absence (a) or presence (b-d) of shunting inhibition. The location of the shunting

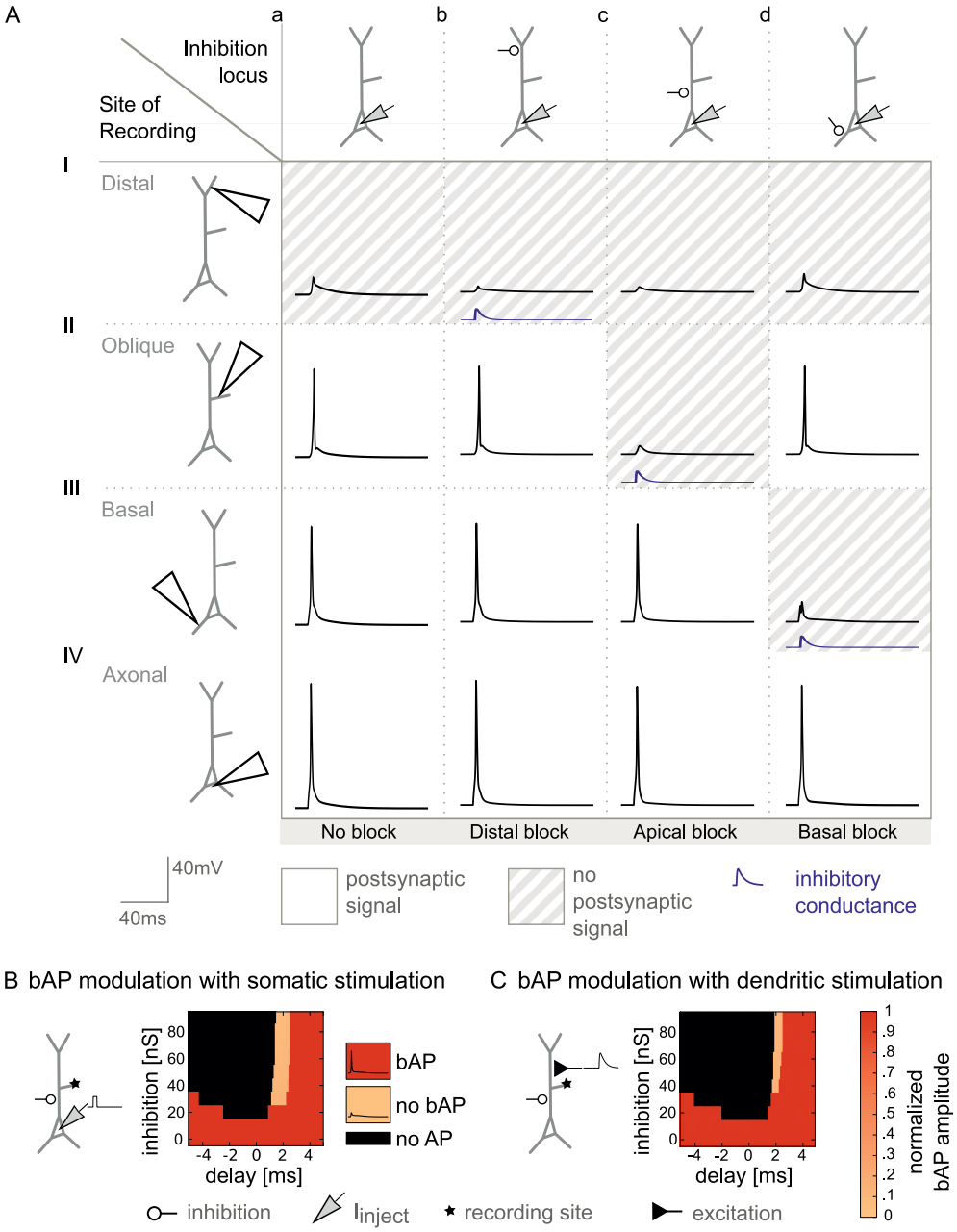


Figure 4.3: **Compartment-specific inhibition of bAPs in the absence of calcium spikes.** A: Effect of inhibition locus on bAPs, elicited by somatic current injection. The recording site varies along the rows; the site of inhibition varies along the columns. Inhibitory conductance is indicated by the blue traces (inhibition onset was 1.5 ms after stimulation onset). a: No inhibition. b: Distal inhibition (460 µm, 50 nS) affected the distal bAP, but did not have a pronounced effect in the absence of a calcium spike (I), it however left signaling in the remaining dendritic tree intact (II and III). c: Proximal inhibition (90 µm, 50 nS) affected signaling in the whole apical dendrite by eliminating the bAP (II), but did not affect the bAP in the basal dendrite (III). *Caption continued on the following page.*

Figure 4.3: d: The bAP in the basal dendrite, and thus basal plasticity, was suppressed by basal inhibition (100 µm, 50 nS) (III), while apical signaling was unchanged (I and II). B: Effect of inhibition onset timing on bAP and calcium spike modulation. Inhibition was shunting with $GABA_A$ time constants (τ_{rise} = 0.5 ms, τ_{decay} = 5 ms). Strength of inhibition varies along each y-axis, onset of inhibition relative to the onset of the somatic step current varies along each x-axis. A: Proximal inhibition on the apical dendrite and its effect on bAPs. The corresponding somatic APs were elicited by somatic step current injection (as in Fig. 4.1C) and peaked around 2.5 ms after stimulation onset. Color-coded is the amplitude of the bAP measured in the oblique dendrite (star indicates recording site). Unless somatic spiking was inhibited (black), either a full-blown bAP (red) or no bAP (light orange) could be observed. C: The neuron was driven by excitatory synapses distributed along the apical trunk to represent inputs from oblique dendrites (see Methods). Modulation of the bAP was possible in a narrow time window.

inhibition varies across the columns of the figure, the site of recording of the voltage trace varies across rows. Compartments where the local bAP was canceled by inhibition (i.e. the remaining voltage amplitude was small) are shaded in gray.

The first column in Fig. 4.3A lays out the voltage traces in the control situation without inhibition, showing an AP in the axon initial segment and related bAPs in the other compartments. Distal inhibition further decreased the already severely attenuated bAP in the distal dendrite, but did not change signaling in the apical oblique and basal dendrites (Fig. 4.3A-b). With inhibition onto the proximal dendrite, the bAP could be barred from the apical dendrite, without affecting the bAP in the basal dendrite (Fig. 4.3A-c). Finally, basal inhibition canceled the bAP in the basal dendrite (Fig. 4.3A-d).

Timing requirements for bAP modulation

To assess whether timing requirements for the modulation of bAPs are realistic, we varied both the strength and the timing of proximal inhibitory inputs and monitored their effect. As discussed above, bAPs were canceled by inhibition in an all-or-none manner. We hence distinguished three cases: (1) inhibition had no effect on the bAP, (2) inhibition canceled the bAP in the dendrite without affecting the somatic spike (the scenario of interest for the modulation of plasticity), and (3) somatic firing was abolished altogether and hence also no bAP was observed. The sensitivity of the bAP to proximal inhibition showed a marked dependence on timing (Fig. 4.3B). The interesting case (2) was observed in a constrained time window of delays between onset of somatic stimulation and onset of inhibition, which was about 1 ms (Fig. 4.3B, light orange area). Given that bAPs are relatively short regenerative events that rapidly invade the dendritic tree, inhibition had to be available at the time of the spike. Additionally, early proximal inhibition could prevent the neuron from firing by suppressing action potential initiation in the axon initial segment, corresponding to case (3) (Fig. 4.3B, black area). Conforming with the local effects of shunting inhibition (Koch et al., 1990; Rall, 1967), distal inhibition had no effect on bAPs in the oblique dendrites (S3 FigB).

Maintaining forward-directed signal flow from excitatory dendritic synapses

So far in the analysis, somatic action potentials depended on somatic current injection. The majority of excitatory inputs, however, arrive on the dendrites. For the hypothesized inhibitory regulation of plasticity not to interfere with neuronal processing, it needs to be ensured that shunting inhibition does not impair the forward flow of signals from the dendrites to the soma (while canceling the bAP). We hence also included conductance-based excitatory inputs to the dendrites.

In the simplest case, inhibition modulates dendritic signals of postsynaptic spiking that was triggered by an excitatory pathway arriving in a different dendritic compartment. This case proved largely identical to direct somatic stimulation, because inhibitory inputs are not on the electrotonic route from the site of excitatory stimulation to the soma. Functionally, postsynaptic activity triggered by synaptic input in one dendritic compartment A could potentially mediate plasticity in a different compartment B. Our results suggest that in this scenario, synaptic plasticity in dendritic compartment B can be readily modulated by inhibitory inputs, by controling the spread of dendritic signals in this compartment.

In a more complex setting, excitatory stimulation and inhibitory control impinge onto the same dendrite. In this case, it is less clear whether inhibition of backpropagating dendritic signals is possible without impairing the ability of forward-directed input integration. A quantitative analysis revealed that an EPSP could reach the soma despite an inhibitory conductance (located 90 µm from the soma) that was capable of suppressing the bAP within a time window of about half a millisecond (Fig. 4.3C). The width of this window, however, depended on the location of inhibition and broadened with increasing distance of inhibition from the soma, swiftly exceeding 1 ms (S4 Fig). The farther inhibition was located from the soma, the more time remained between the passage of a forward-directed EPSP and the arrival of a bAP at the site of inhibition, resulting in an increase of the time window. Functionally, this scenario applies to the case where postsynaptic activity triggered by input onto a given dendritic compartment mediates plasticity in the same compartment. Our results suggest that an inhibitory modulation of this form of plasticity is possible, but requires a precise timing of inhibition.

4.2.3 Inhibition of bAPs and calcium spikes during BAC firing

While many neurons exhibit bAPs, some neuron types (such as cortical layer 5 and CA1 pyramidal neurons) can additionally generate distal calcium spikes that trigger BAC firing. Because calcium spikes can also serve as plasticity signals (Golding et al., 2002), we analyzed the effects of inhibition on bAPs and calcium spikes during this firing mode. To trigger calcium spikes in the distal dendrite, we here combined somatic current injection in our model with coincident depolarization in the distal dendrite.

In the control situation without inhibition (Fig. 4.4A-a), a calcium spike was triggered in the distal dendrite and the resulting BAC-firing-induced bursts of APs could be observed in the other compartments. Calcium spikes (and the accompanying burst of APs) proved highly sensitive to inhibitory inputs in the distal part of the apical dendrite (Fig. 4.4A-bI). In contrast, the bAP was relatively robust to distal inhibition and readily invaded both the apical oblique and basal dendrites despite the presence of

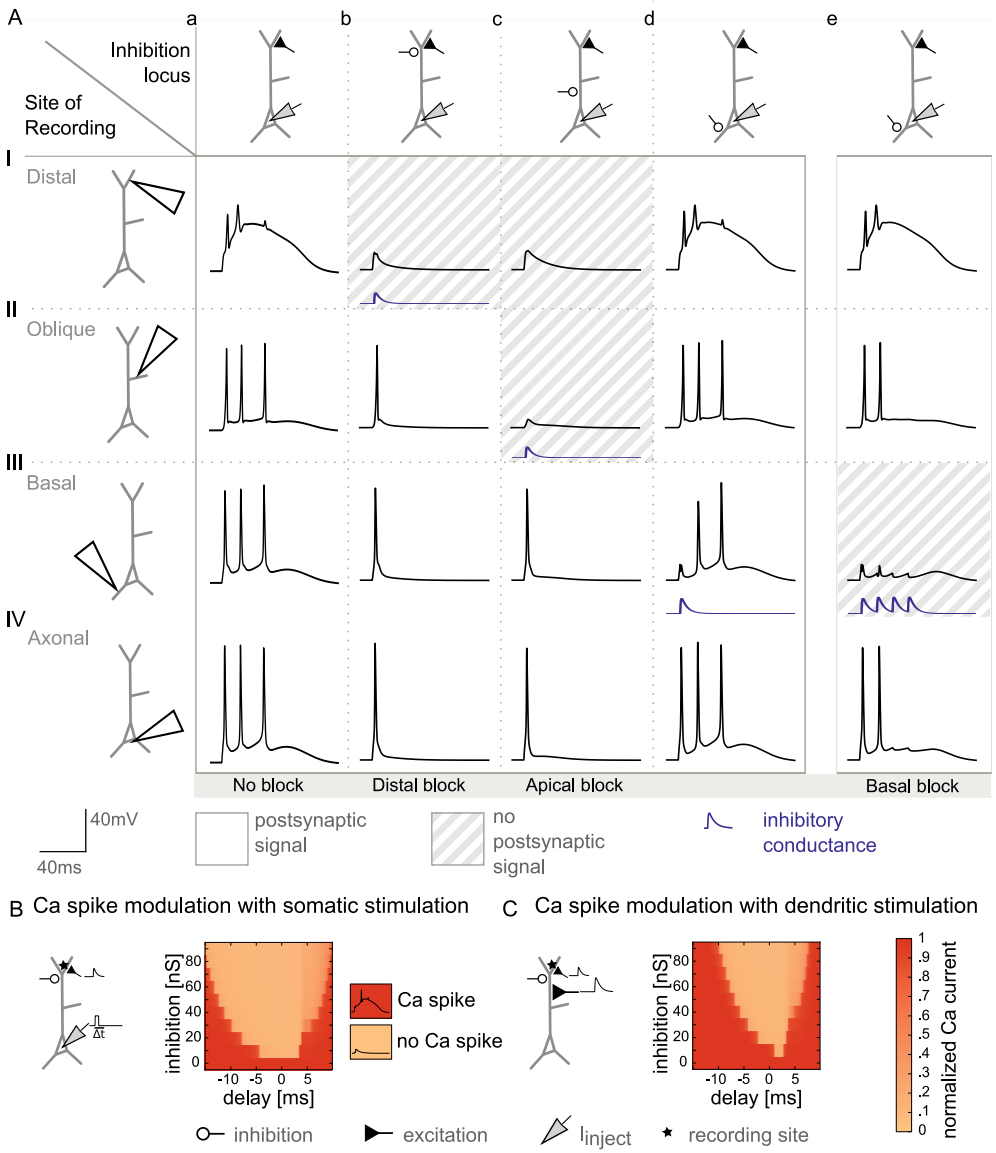


Figure 4.4: **Compartment-specific inhibition of bAPs and calcium spikes during BAC firing.** A: Effect of inhibition locus on dendritic coincidence signals, when somatic current injection was paired with dendritic excitation (with a delay Δt of 0 ms) to trigger a calcium spike (as in Fig. 4.1D). As in Fig. 4.3A, the recording site varies along the rows; the site of inhibition varies along the columns. Inhibitory conductance is indicated by the blue traces (inhibition onset was 1.5 ms after stimulation onset). a: No inhibition. b: Distal inhibition (460 µm, 50 nS) suppressed the calcium spike (I) and thus distal plasticity, but left signaling in the remaining dendritic tree intact (II and III). c: Proximal inhibition (90 µm, 50 nS) affected signaling in the whole apical dendrite by eliminating the bAP (II), and thus the calcium spike (I), but did not affect the bAP in the basal dendrite (III). *Caption continued on the following page.*

Figure 4.4: d: In the presence of a calcium-spike induced somatic burst, one inhibitory pulse was not sufficient to block the propagation of all bAPs into the basal dendrite (III). e: The train of bAPs in the basal dendrite, and thus basal plasticity, was suppressed by four inhibitory conductance changes at a frequency of 75 Hz on the proximal basal dendrite (100 µm, 70 nS) (III), while apical signaling was unchanged (I and II). B: Inhibition of calcium spikes in the distal apical dendrite. Calcium spikes were triggered by coincident bAPs and distal excitation with a temporal separation (Δt) of 0 ms (as in A). Color-coded is the calcium transient in the apical tuft, normalized to its uninhibited value. While the bAP could be modulated by proximal inhibition within a time window of 1 ms (Fig. 4.3B), calcium spikes were rather insensitive to timing, and were abolished by weak distal inhibition. C: Inhibition of calcium spikes in the distal apical dendrite, when the neuron was driven by excitatory synapses distributed along the apical trunk to represent inputs from oblique dendrites (see Methods). The EPSPs were paired with distal excitation with a temporal separation (Δt) of 0 ms. As in B, the calcium spike could be modulated, less dependent on timing than the bAP.

distal inhibition (Fig. 4.4A-bII/III). In the basal dendrite, inhibition was not sufficient to cancel all BAC firing related bAPs, because the single $GABA_A$ conductance decayed too fast, and hence could not exert an influence on later bAPs (Fig. 4.4A-dIII). bAPs in the basal dendrite could, however, be controled by inhibition that outlasted the burst. Such inhibition could be mediated by inhibitory synapses of the same dynamics but an activation that is distributed in time (as it could be provided by bursting interneurons). Along these lines, four temporally spread out inhibitory inputs were able to cancel the bAPs in the basal dendrite (Fig. 4.4A-eIII). The quantitative dependence of this effect on frequency and number of such repetitive inhibitory inputs is shown in S2 Fig. Altogether, we have seen that, in principle, inhibition can cancel coincidence signals in a manner that is selective between compartments.

Different time scales for bAP versus calcium spike modulation

Next, we explored the timing requirements for inhibition to cancel the coincidence signals in the BAC firing mode. Despite the distal depolarization, the width of the timing window for bAP modulation remained unchanged (S3 Fig). The time window where inhibition could cancel a calcium spike, however, was broader (>5 ms) than the corresponding window for bAP cancelation (~1 ms). Compared to bAP modulation, smaller inhibitory conductances were sufficient to block calcium spikes in the distal tuft.

4.2.4 Robustness to morphology

To demonstrate the robustness of our results with respect to morphological and physiological detail, we replicated the main findings in an anatomically reconstructed L5 neuron model with different physiology (Hay et al., 2011) (Fig. 4.5).

4.2.5 Compartment-specific inhibition and plasticity

To demonstrate that cancelation of the coincidence signals indeed results in the anticipated changes to synaptic plasticity, we next subjected the model cell to a classical

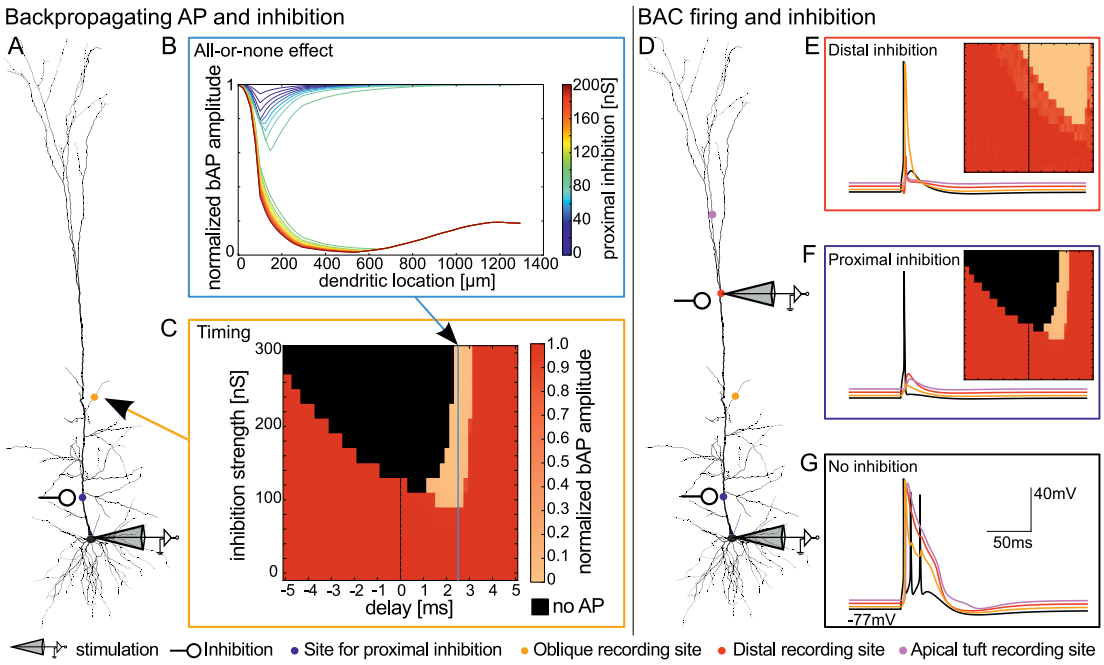


Figure 4.5: **Validation of results in a model cell with anatomically reconstructed morphology.** This model was previously fitted to account for BAC firing by Hay and colleagues (Hay et al., 2011). Using their original parameters, we replicated the all-or-none modulation of bAPs by proximal inhibition (B), the compartmental modulation of bAPs versus calcium spikes in the morphologically complex dendrite (E-G), and the required time scales for proximal versus distal inhibition (C,E). Ionic conductances in the model by Hay et al. differed from those used in our simplified pyramidal cell model. We found the recovery of the bAP to be independent of the exact ion channel composition of the dendrite, as long as the interplay of sodium and counteracting currents allowed for an active propagation of the sodium spike. A: Morphology of the neuron. Somatic current injection as in (Hay et al., 2011) was used to elicit a bAP. Sites of proximal inhibition (blue) and oblique recording (yellow) are indicated. B: All-or-none modulation of the bAP along the apical dendrite, from the soma into the very distal apical tuft. C: Timing and strength of proximal inhibition (x- and y-axis, respectively) and its effect on the bAP amplitude in the oblique dendrite. Color-code as in Fig. 4.3B/C. D: Somatic current injection paired with dendritic stimulation as in (Hay et al., 2011) was used to trigger BAC firing. Sites of proximal inhibition (blue), distal inhibition and recording (red), and apical tuft (pink) and oblique (yellow) recording are indicated and correspond to colored voltage traces in E to G. E: Distal inhibition inhibited BAC firing, but did not inhibit the bAP in the oblique dendrite. Inhibition of the calcium spike could be achieved for a range of timings (inset, same axes and color code as in B). F: Proximal inhibition inhibited the bAP in the oblique dendrite and BAC firing, if timed appropriately (inset). G: Without inhibition, pairing of bAP and distal input results in BAC firing (Hay et al., 2011).

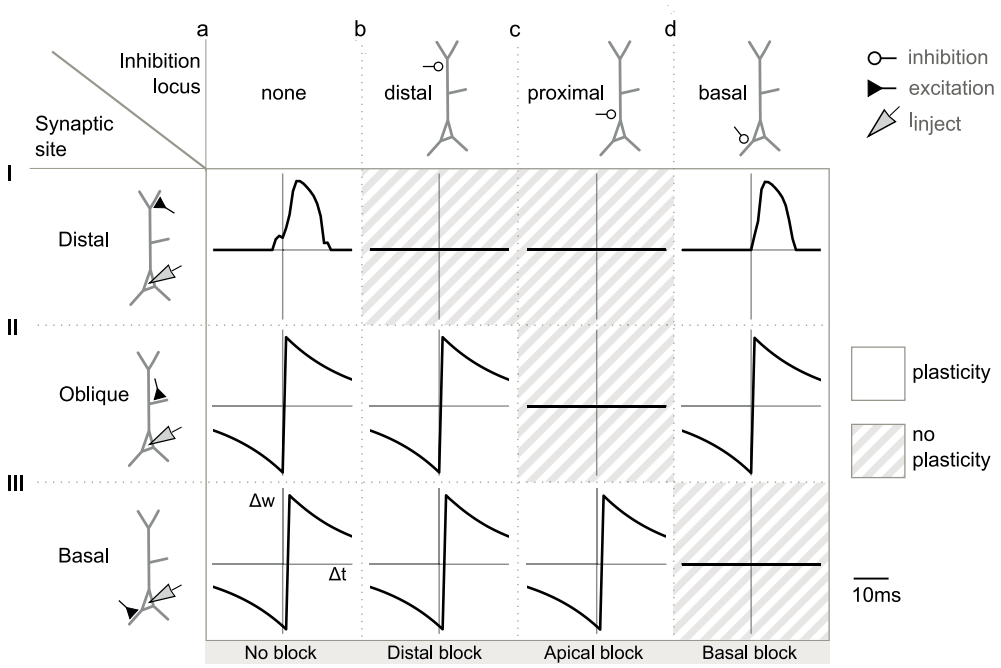


Figure 4.6: **Switching STDP learning rules by inhibition of dendritic signals in a compartment-specific manner.** Results are presented in the same format as in Fig. 4.3A. For each synaptic location, a somatic step current was paired 100 times at 1 Hz with the synaptic activation at different Δt, to simulate a pairing protocol, and to measure the resulting plasticity rule. Inhibition was placed at different locations on the dendritic tree, inhibition onset was 1.5 ms after stimulation onset, rise and decay time constants were 0.5 ms and 5 ms, respectively, the maximum conductance amounted to 50 nS. Synaptic change was normalized to its maximum. A: No inhibition. B: Distal inhibition on the apical dendrite led to a flat STDP window in the distal synapse. C: Proximal inhibition on the apical dendrite caused zero synaptic change in both oblique and distal synapses. D: Proximal inhibition on the basal dendrite abolished STDP in the basal synapse.

plasticity paradigm. Contemporary biophysical and phenomenological models of STDP (Clopath et al., 2010; Graupner and Brunel, 2007; Shouval et al., 2002; Song et al., 2000) depend on postsynaptic variables such as depolarization or calcium concentration, which are in turn shaped by bAPs and calcium spikes. Because the latter can be abolished by properly timed and placed inhibition, we suggest that cancelation of these signals via inhibition will lead to a noticeable change in the predicted learning rule (or abolish plasticity altogether). To demonstrate this, we simulated a typical STDP pairing protocol (see, for example Bi and Poo, 1998; Sjöström et al., 2001). Somatic current injection was paired with excitatory synaptic activation on either basal, oblique, or distal dendrites with a time delay Δt. Excitatory synaptic plasticity was Hebbian with a positive weight change for positive timings between the activation of the synapse and the arrival of a depolarizing postsynaptic potential and a negative weight change for negative timings (for details see Methods). We implemented the simple additive rule by (Song et al., 2000), leading to the classical asymmetric STDP window (Fig. 4.6). While the learning windows for oblique and basal synapses resembled the classical one (Fig. 4.6II/III), we found the distal learning window to be more symmetric (Fig. 4.6I). The latter results from the assumption that at distal synapses a calcium spike serves as the signal for plasticity. Because a calcium spike required the coincidence of bAP and EPSP, a calcium spike could only occur (see Methods) after presynaptic activation, such that the synaptic change was positive unless the relative timing of bAP and EPSP did not lead to a calcium spike (in which case it was zero). As expected, inhibitory cancelation of bAPs and calcium spikes in the dendrite resulted in flat learning windows, corresponding to zero synaptic change (compare Fig. 4.3A/4.4A and Fig. 4.6). Because of the all-or-none effect of inhibition on dendritic signals, we predict a switch-like effect on learning for any plasticity rule relying on the coincidence of pre- and postsynaptic spiking.

4.2.6 How to satisfy the timing constraints for the inhibitory modulation of bAPs

Above, we have shown that the modulation of the bAP requires inhibition to fall into a small time window closely tied to the initiation of the somatic action potential in the pyramidal neuron. The question arises whether such timing is realistic and how it can be achieved. As a proof of principle, we here show that the common local circuit motif of feedforward inhibition (Callaway, 2004) is a good candidate to provide the appropriate timing. In feedforward inhibition an excitatory signal is passed on to a pyramidal neuron along two parallel pathways: one direct excitatory pathway to the pyramidal cell and one indirect pathway, where the signal first excites an inhibitory neuron that sends its output on to the pyramidal cell (see Fig. 4.7A, black parts of the schematic representation). From the perspective of the pyramidal neuron, excitation in this circuit arrives first to be followed by a delayed inhibition (Pouille and Scanziani, 2001). Embedding our pyramidal cell model into this circuit we found that inhibition arriving 2 ms after the EPSP was suited to control the bAP signal (Fig. 4.7B, Δt = 2 ms). This delay matched experimentally measured inhibition delays well (Pouille and Scanziani, 2001; Wehr and Zador, 2003) and was suited to control backpropagation without affecting forward-directed signal flow responsible for the

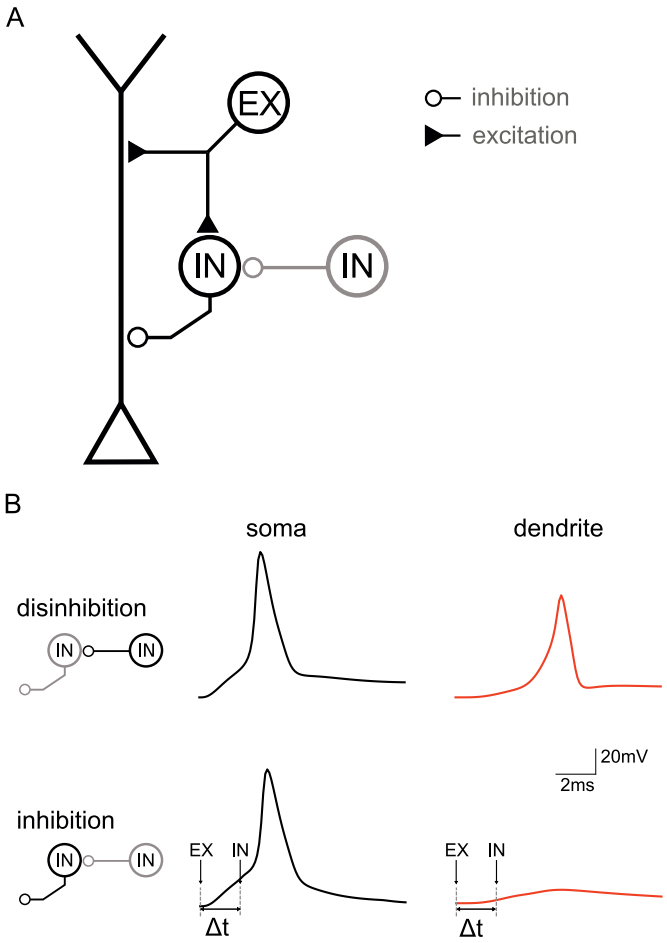


Figure 4.7: **Circuit model of feedforward inhibition.** A: Topology of the circuit with a multicompartmental pyramidal neuron model and a model of a fast-spiking inhibitory interneuron (IN, targeting pyramidal neuron) receiving excitatory input from a source (EX) at time t_0 and potentially tonic disinhibition (IN, targeting IN). B: Effect of switching the feedforward interneuron on and off (via a second interneuron - marked gray in panel A) measured in the dendrite of the pyramidal neuron (370 µm from the soma), which in turn is driven by apical excitation. Note that the circuit is identical to that in panel A, although the lefthand schematics only zoom in on the interneurons. Upper paradigm: When the feedforward interneuron is switched off (in gray) because of activation of the second interneuron (in black), excitation triggers a spike in the pyramidal cell's soma which propagates unhindered into the dendrite. Lower paradigm: When the feedforward interneuron is active (in black) due to excitation and because the second interneuron is switched off (in gray), excitation triggers a spike in the pyramidal cell's soma that does not propagate far into the dendrite due to the inhibition provided by the feedforward interneuron (90 µm from soma, $\Delta t = 2$ ms).

initiation of postsynaptic somatic spikes.

Interestingly, interneuron dynamics play a role for the timing requirements. Dependent on interneuron type, spike latencies and firing frequencies can vary. The size of the temporal window where inhibition can cancel bAPs (without canceling EPSPs) tends to be smaller for proximal inhibitory synapses than more distal synapses, as outlined above. One may hence speculate that the dynamics of interneurons innervating proximal parts of the dendritic tree should be sufficiently fast. To highlight the role of interneuron dynamics, we probed the circuit with two interneurons differing in their spiking dynamics. We used the interneuron model from the previous paragraph and compared its performance in the circuit to that of a second interneuron with slower dynamics. The latter was implemented by artificially slowing down the opening and closing rates of the interneuron's sodium channels. In this example, only the interneuron with a short spike latency met the tight timing requirements for bAP modulation at a more proximal synaptic location (S6 FigA). The timing provided by the slower interneuron did not suffice to cancel the bAP proximally. In contrast, both (faster and slower) interneurons were able to cancel the bAP (and the accompanying calcium spike) when their synapses were located at more distal parts of the dendritic tree (S6 FigB).

4.3 Discussion

In this study, we investigate how dendritic inhibition can serve to regulate Hebbian plasticity of excitatory synapses. Using multi-compartmental biophysical neuron models, we show that shunting inhibition can gate the propagation of bAPs as well as dendritic calcium spikes in an all-or-none manner and thus exert direct control over the Hebbian coincidence signals. As a functional consequence, inhibition can provide a binary switch of synaptic plasticity. This switch can be specific for pathways in the local network as well as subsets of synapses within the same neuron. Importantly, forward-directed information flow via orthodromic EPSPs can be maintained when bAPs and calcium spikes are annihilated by shunting inhibition. The trivial scenario, where inhibition cancels not only Hebbian coincidence signals but also the excitatory drive of the neuron, can hence be avoided. Quantitative analyses of the physiologically constrained models reveal that this mechanism imposes strict timing constraints: while for the regulation of bAPs inhibition has to fall into a specific time window of a width of 1 ms, regulation of calcium spikes requires less precise timing. The time scales for proximal and distal inhibitory modulation of plasticity differ by several milliseconds. Finally, we suggest and provide a proof of principle that the precise timing required for bAP modulation can be achieved by a local circuit including the common network motif of feedforward inhibition.

4.3.1 A functional role for inhibition in the context of plasticity

The central hypothesis that inhibition can control synaptic plasticity has been discussed in the experimental and theoretical literature (Bar-Ilan et al., 2012; Häusser and Mel, 2003; Marlin and Carter, 2014; Paulsen and Moser, 1998; Saudargiene et al., 2015; Tatsuya et al., 2013). Its feasibility and functional relevance relate to three observations.

First, different compartments within a neuron often receive excitatory input from distinct synaptic pathways (Spruston, 2008), such that a compartment-specific regulation of plasticity could be functionally advantageous. Second, different compartments are targeted by different inhibitory interneuron classes (Klausberger, 2009; Markram et al., 2004), so that Hebbian coincidence signals could be regulated locally. Third, dendrites support different plasticity-related coincidence signals, namely bAPs (Markram, 1997; Sjöström et al., 2008) and calcium spikes (Golding et al., 2002; Larkum et al., 1999b; Schiller et al., 1997), which are sensitive to inhibitory control (Buzsáki et al., 1996; Larkum et al., 1999b; Miles et al., 1996; Murayama et al., 2009; Tsubokawa and Ross, 1996). Besides a switch in plasticity, inhibition has been shown to contribute to the shape of temporal requirements for plasticity in different parts of the dendrite (Cutsuridis, 2011; Saudargiene and Graham, 2015; Tsukada et al., 2005). Moreover, the induction and coincidence requirements of plasticity have been described to change with development, potentially through an increase in inhibition (Groen et al., 2014; Hensch et al., 1998; Meredith et al., 2003).

Strong experimental evidence in support of the ability of inhibition to modulate plasticity via gating of bAPs was recently provided by Müllner et al. (2015) (Müllner et al., 2015). They showed that one important step in this mechanism—the suppression of somatically elicited bAPs by dendritic inhibitory synapses with high temporal precision—is indeed possible. For a robust switch of plasticity, however, several points remain to be shown: (1) gating of coincidence signals can be exerted in a controlled and systematic manner, (2) forward information flow via EPSPs can be maintained, and (3) plasticity itself is altered. Our analysis on the basis of mathematical models with physiologically constrained properties demonstrates that all three points can be fulfilled. In particular, we find that shunting inhibition is sufficient to cancel bAPs and calcium spikes while preserving the ability of EPSPs to elicit somatic APs. Timing of inhibition needs to be precise, but is not unrealistic (~1 ms for bAPs and $>$5 ms for calcium spikes).

4.3.2 Model-derived predictions

Our study makes several testable predictions. In particular, the all-or-none nature of bAP modulation enabling the binary switch as well as the compartment specificity could be tested in experiments. To investigate the latter, classical paired recording paradigms for synaptic plasticity could be extended by optogenetic stimulation of different interneuron classes. Particularly promising candidates are the above mentioned SOM or PV interneurons that target perisomatic and distal dendritic regions of pyramidal cells, respectively (Klausberger, 2009; Markram et al., 2004).

Moreover, perisomatic versus distal modulation of dendritic coincidence signals poses different timing requirements on inhibition. The proximity of inhibition to the soma constrains the modulation window, because the times of passage of the forward-directed EPSP and the backward-directed bAP (at the location of the inhibitory synapse) are very close. Therefore, inhibitory synapses ought to have a certain distance to the soma to be well suited to control the bAP and plasticity without canceling somatic spiking. Our results suggest that at a distance of ~100 µm, which is relatively proximal for apical dendrites, the timing window becomes wide enough to enable

inhibitory control (S4 Fig). We predict that the regulation of bAPs caused by more proximal excitation in the pyramidal neuron may be better achieved by interneurons with short latencies, such as fast-spiking interneurons. We found that distal inhibition of the calcium spike did not require very precise timing and tolerated longer delays to the onset of shunting inhibition. In the context of the here discussed mechanism of plasticity regulation, it would be functionally useful if proximal and distal inhibition were accomplished by interneurons of different dynamics. This proposition is in line with the fact that the many interneuron types connected to pyramidal cells differ in their spiking dynamics as well as their dendritic target location in pyramidal cells. Regulation of calcium spikes in the distal dendrite, on the other hand, need not be provided by local circuits, but could be mediated by longer-range connections including multiple synaptic transmissions. One may speculate that this timescale is beneficial when incorporating top-down information that tends to arrive in superficial layers (Larkum, 2013).

From the perspective of the pyramidal neuron, we find that a short rise time of synaptic inhibition (like that typical for $GABA_A$-mediated inhibition (~0.5 ms) is crucial for the mechanism to operate effectively. In contrast, the temporal extent of inhibition (determined by the temporal extent of inhibitory input as well as the decay time constant of inhibition) is less important. These variables are likely to be more relevant in setting a lower frequency limit to excitatory signals because they could interfere with a following EPSP if inhibition lasted for too long. For $GABA_A$-typical decay time constants on the order of 5 ms (as used here), such limits to the frequency of EPSPs are sufficiently large (>100 Hz). We note that $GABA_A$-mediated inhibitory postsynaptic potentials (IPSPs) have been described to differ between proximal and distal sites (Turner, 1990). The difference is mainly in half-width and decay time constant, less in rise time. We hence used the same time constants for proximal and distal $GABA_A$-mediated currents.

Our results suggest that, in contrast to the other compartments, in basal dendrites several volleys of interneuron input may be needed to suppress all bAPs. In this scenario, a burst of bAPs invades the dendrite in the BAC firing mode. For this compartment, an innervation by bursting interneurons may hence be advantageous and several bursting interneuron types, including double bouquet cells (Kawaguchi and Kubota, 1997) and bistratified cells (Buhl et al., 1996; Katona et al., 2014; Klausberger et al., 2004), have been described.

Our prediction on the timing dependence of the modulation of bAPs quantitatively agrees with the experimental study by (Müllner et al., 2015). They found that calcium transients, evoked by a train of bAPs, are maximally inhibited with a spike timing (between interneuron and pyramidal cell) on the order of < 5 ms. This timescale is compatible with our predictions for the required timing of bAP modulation (see Fig. 4.3B/C). Also space constants of inhibition, observed to be on the order of 23-28 µm by Müllner and colleagues, are comparable to our results (see Fig. 4.2).

4.3.3 Implications of feedforward inhibition

As our study showed, inhibition has to fall into a narrow time window to gate APs without simultaneously canceling EPSPs that are meant to drive the postsynaptic cell,

potentially casting some doubt on the robustness of the mechanism of an inhibition-mediated plasticity switch. Feedforward inhibition, however, seems a good candidate to guarantee the appropriate timing, in particular, as in such a circuit inhibition follows excitation within a relatively fixed time interval. Feedforward inhibition is a common circuit motif (Buzsáki, 1984; Gupta et al., 2000) that has, for example, been implicated in keeping a balance of excitation and inhibition and to open time windows for precise firing events (Owen et al., 2013; Pouille and Scanziani, 2001; Wehr and Zador, 2003). While we do not suggest that it is the only mechanism that can provide suitable timing for the plasticity switch discussed here, it can satisfy both temporal requirements for the cancelation of bAPs: the delay between forward-directed excitation and the shunting inhibition, as well as the temporal precision on the order of a millisecond. In the circuit model (Fig. 4.7A, black part of the schematic), a delay on the order of 2–3 ms between onset of the excitatory EPSP and the onset of the inhibitory IPSP in the pyramidal neuron was required to cancel the bAP triggered by the EPSP. This delay has to be accounted for by the processing in the inhibitory neuron itself and comprises the time the EPSP *in the interneuron* needed to reach this neuron's soma, spike generation in this cell, propagation of the action potential along the axon, and the inhibitory synaptic transmission between interneuron and pyramidal cell. The timescale of 2–3 ms is plausible for these processes and agrees with the range reported in experiments (Pouille and Scanziani, 2001; Wehr and Zador, 2003). Characteristics of the interneuron allow for some flexibility of this delay (Bartos et al., 2011). For example, a fast spike generation (as in fast-spiking interneurons, due to lower firing threshold and/or stronger excitation on interneurons (Cruikshank et al., 2007; Gabernet et al., 2005)) plays an important role in keeping the delay short. Additionally, dendritic propagation is slower than axonal propagation, so that the relative length of these cables influences the required delay (which may potentially be correlated to the somatic location of the interneuron, assuming a regular, bipolar morphology where the soma lies in-between dendrites and axon). For example, a more proximal excitation in the pyramidal neuron requires a shorter delay of inhibition. The integration time in the pyramidal neuron depends on the location, and distribution of synaptic excitatory inputs, next to being negatively proportional to the number, strength and rise time of the synaptic conductances.

In a feedforward inhibitory circuit, inhibition, by default, comes along with excitation. This means that an additional source is required to switch off the inhibitory influence (see Fig. 4.7A, gray part of the schematic). *Per se*, when the interneuron is *active*, plasticity of excitatory pyramidal synapses is switched off. In turn, *silencing* the interneuron up-regulates pyramidal cell plasticity. This design indicates a disinhibitory regulation of Hebbian plasticity, which is in line with recent findings for behavioral learning (Letzkus et al., 2011; Lovett-Barron et al., 2014). Interestingly, advances in unraveling the connectivity profile of different interneuron classes suggest that the cortical mircocircuitry seems to be well suited for a disinhibitory and compartment-specific regulation (Higley, 2014; Lee et al., 2013; Marlin and Carter, 2014; Pfeffer et al., 2013; Pi et al., 2013). In particular, vasoactive intestinal peptide (VIP) expressing interneurons and other supragranular interneuron classes have been proposed to modulate the activity of somatostatin (SOM)- and parvalbumin (PV)- positive cells – inhibitory interneurons with distinct postsynaptic targets within the pyramidal dendrite – in a

way that is consistent with a rapid redistribution of inhibition between perisomatic and distal apical dendrites of pyramidal cells (Cottam et al., 2013; Pfeffer et al., 2013).

4.3.4 Other forms of synaptic plasticity

We note that distal disinhibition in pyramidal cells is special because it can significantly and reversibly increase the occurrence of calcium spikes and somatic bursts (Gentet et al., 2012). Calcium-induced bursting has been proposed as a mechanism for the association of inputs arriving through different pathways (Larkum, 2013). Because synaptic plasticity is often more efficiently induced by pairing presynaptic inputs with postsynaptic bursts, it is tempting to speculate that calcium spikes can induce a form of global synaptic plasticity within a neuron. Consequently, plasticity in the entire dendritic tree could be regulated at a single spot through local disinhibition. Note that such a form of plasticity regulation does not exclude, but complements our main hypothesis, because proximal inhibition could contribute to impair the arrival of bursts of backpropagating APs at basal and oblique synapses (see Results on basal signaling). However, our prediction that basal plasticity regulation requires more complex inhibitory innervation in the presence of a calcium spike, possibly indicates that calcium-dependent burst firing is in place to overcome the effects of inhibition by increasing the likelihood of backpropagating action potentials passing the barrage.

STDP is an important and commonly observed mechanism underlying many forms of learning (Feldman, 2012). Regulation of STDP (a potential mechanism is considered in this study) is hence highly relevant. However, there are other, non-Hebbian forms of synaptic plasticity which are independent of postsynaptic spiking. For example, plasticity can be directly triggered by spikes of dendritic origin that arise locally from cooperative or strong synaptic activation (Golding et al., 2002). The proposed pathway-specific switch does not apply to these types of plasticity. Still, theoretical and experimental studies have shown that dendritic spikes can be affected by inhibition on a local (spine- or branch-specific) or global level (Gidon and Segev, 2012; Jadi et al., 2012; Müller et al., 2014), possibly providing a mechanism to control timing-independent plasticity. Especially NMDA spikes cannot be excluded as a target for inhibitory modulation. Because they present a more local phenomenon that carries limited information about somatic spiking, an investigation thereof is beyond the scope of the present study. One kind of synaptic plasticity which is unlikely to be regulated by inhibition of dendritic events at all is presynaptically induced and expressed LTD (Tzounopoulos et al., 2007).

4.3.5 Conclusion

In this study, we provide computational evidence that the known physiological characteristics of pyramidal cells are sufficient to exert a binary control of plasticity while preserving excitatory, forward-directed information flow. Despite the fact that the identified timing requirements for this mechanism may at first seem tight, the proposed local circuit motif of feedforward inhibition seems well suited to provide inhibition at appropriate times. Our modeling work substantiates the point of view that inhibition is likely to play a crucial role for Hebbian plasticity of excitatory synapses in a manner that can be specific to individual pathways of the local network(Paulsen and

Moser, 1998). Recent advances of optogenetic methods allow to shed further light on the computational relevance of interneuron diversity (Larkum, 2013; Lee et al., 2013; Müller and Remy, 2014; Pi et al., 2013) and could—by targeting specific interneuron types—help to reveal whether (and if so which) neurons can regulate plasticity in local circuits.

4.4 Methods

4.4.1 Simplified morphology model

Morphology and passive parameters

Simulations were performed in NEURON (Hines and Carnevale, 1997), with an integration time step of 0.1 ms and a temperature of 30 °C. The neuron consisted of an axon initial segment (2 µm in diameter, 3 µm in length, nseg=1), soma (diameter and height 18.5 µm, nseg=1), an apical dendrite, and a basal dendrite (Fig. 4.1A). The apical dendrite had a main shaft (diameter 2 µm), first- and second-order branches (2/3 of the diameter of their respective mother branch). In addition to the distal branches, an oblique dendrite was joined to the apical trunk 100 µm from the soma, dividing the trunk into two compartments, a 100 µm long compartment (nseg=19) and a 400 µm long compartment (nseg=73). Its total length hence amounted to 500 µm, while all other branches had a length of 300 µm (nseg=91). Basal dendrite parameters were: main shaft diameter 1 µm, daughter branches 2/3 of their mother branches, length 150 µm for all basal dendrites (nseg=91). Second-order branches were added to prevent boundary effects, but not specifically studied; they are not shown in the schematic figures. The passive parameters of the neuron were: membrane capacitance C_m=0.75 µF/cm^2, axial resistivity R_a=150 Ωcm, and membrane resistance R_m=40,000 Ωcm^2; leak reversal potential E_L=-70 mV. The simulation code is available in the ModelDB database under the accession number 187603 (https://senselab.med.yale.edu/ModelDB/).

Active Conductances

Both the neuron and its dendrites hosted active conductances to allow somatic and dendritic action potentials. The voltage-dependent conductances were limited to those needed for the occurrence of backpropagating action potentials and calcium spikes as experimentally observed. In a first step, inactivating sodium and delayed-rectifying potassium conductances with channel kinetics from (Migliore et al., 1999) (ModelDB accession 2796) were adjusted in density such that bAPs propagated within the dendritic tree with a stable amplitude. The spatial distribution of these conductances was uniform (Magee and Johnston, 1995). To account for the attenuation of the bAP (Hoffman et al., 1997), A-type potassium channels (ModelDB accession 2796, kaprox.mod, (Migliore et al., 1999)) were added in a second step, with linearly increasing density from soma to distal dendrites. The three conductances and the spatial distribution of the A-type potassium channels were fitted such that the model output matched experimentally observed bAP attenuation in CA1 pyramidal cells (Spruston et al., 1995). Dendritic sodium and delayed-rectifier potassium channels were distributed uniformly with a maximum conductance of 0.009 S/cm^2 and 0.01 S/cm^2, respectively. The voltage

dependence of dendritic sodium channel activation was shifted by +5 mV to allow apical excitatory postsynaptic potentials (EPSPs) to cause somatic spikes without eliciting dendritic spikes. The reversal potentials were: E_{Na} = +60 mV and E_K = -80 mV. The A-type potassium conductance increased five-fold up to 500 µm from the soma with an initial value of 0.029 S/cm^2.

To account for calcium spikes, a calcium spike initiation zone with increased calcium channel densities in the apical tuft between 500 and 750 µm from the soma was incorporated. While high-voltage activated calcium channels (Ca,H), a calcium-activated potassium current (K,Ca) and a calcium decay mechanism were present in all dendritic compartments, we added low-threshold T-type calcium channels (Ca,L) only to the active zone. All channel kinetics were taken from (Schaefer et al., 2003) (ModelDB accession: 83344), who adapted the calcium currents from the pyramidal cell model of (Mainen and Sejnowski, 1996). The dendritic channel distributions outside the spike initiation zone were (in S/cm^2): $g_{Ca,H}$ = 0.00015, $g_{K,Ca}$ = 0.00025 and inside: $g_{Ca,H}$ was increased 3-fold, $g_{Ca,L}$ = 0.005. In the soma, $g_{Ca,H}$ and $g_{K,Ca}$ were increased 2-fold compared to the dendrite. The reversal potential for calcium was E_{Ca} = +140 mV.

Axonal spike initiation zone

The axon initial segment consisted of only a single compartment with increased sodium channel density compared to dendritic compartments (0.6 S/cm^2 in total), matching the order of magnitude of the experimentally measured value (2,500 pS/µm^2 = 0.25 S/cm^2) based on modern sodium imaging techniques (Kole et al., 2008)). Voltage dependencies were shifted in 50% of the axonal sodium channels by -10 mV (Colbert and Pan, 2002; Fleidervish et al., 2010; Hu et al., 2009; Turner et al., 1991).

Stimulation protocol and synaptic inputs

If not otherwise indicated, the simplified model was stimulated by somatic step current injection of 0.3 nA for 2 ms. All synapses were modeled as time-dependent conductance changes. The dendritic synapse in Fig. 4.1 (530 µm) had a double exponential time course (a NEURON Exp2Syn synapse with rise and decay time constants of 0.5 and 2 ms, respectively). A maximum conductance of 8 nS was required to trigger a calcium spike in the presence of a bAP. The stronger synapse in Fig. 4.1E had a maximum conductance of 14 nS. In Fig. 4.3C and Fig. 4.4C, the neuron was driven by eight excitatory synapses (Exp2Syn) of the same type distributed equally between 140 and 420 µm, i.e. between the oblique dendrite and the main branching site, representing inputs arriving from putative oblique dendrites. The total maximum conductance of these synapses amounted to 20 nS. Plastic dendritic excitatory synapses in either the basal dendrite (middle of main shaft: 75 µm), the oblique dendrite (middle: 250 µm), or the apical tuft (530 µm) had an exponential time course with reversal potential 0 mV and time constant 3 ms. As in Fig. 4.1, the apical tuft synapse had a maximum conductance of 8 nS as this was required to trigger a calcium spike. The other plastic synapses were initiated with small maximum conductances of 0.001 nS.

Inhibition was modeled to resemble $GABA_A$-mediated, and not $GABA_B$-mediated inhibition, because the former is more abundant, and its time constants are better suited for the task. The large time constants of $GABA_B$-mediated inhibition are not

well suited, because they lead to (1) slow inhibition, which cannot fulfill the tight timing constraints for bAP inhibition, and (2) long-lasting inhibition, which, next to being a waste of energy, can interfere with subsequent signaling. GABAergic inhibition had a double-exponential time course (NEURON Exp2Syn synapse; rise and decay time constants 0.5 and 5 ms, respectively). The reversal potential of the inhibitory synapses was close to the resting potential, i.e. -73 mV. At rest, inhibition hence did not hyperpolarize the membrane potential, but acted as a local "shunt", i.e. increased the membrane conductance. The maximum conductance, referred to as inhibition strength, and the onset of inhibition was varied as indicated.

For control, inhibitory synapses were distributed in space and time according to a Gaussian distribution with varying standard deviation sigma. The spatial distribution was centered around 90 µm and truncated such that synapses were restricted to the apical trunk. The temporal distribution of inhibition onsets was centered around 2 ms after the onset of somatic stimulation.

4.4.2 Spike detection

To study the impact of inhibition on dendritic spikes, we recorded the membrane voltage in the basal dendrite (75 µm), the oblique dendrite (370 µm) and the apical tuft (650 µm). Additionally, we monitored the calcium current in the apical tuft at the same spot. Spike amplitudes were measured as the maximum voltage deviation from rest (a membrane voltage reaching 10 mV would be a spike of amplitude 10 mV-(-73 mV)=83 mV). bAPs were normalized to the non-inhibited amplitude of the first bAP. Calcium spikes were quantified by the integral of the calcium current (to clearly disambiguate between calcium and sodium components of the voltage trace at the same spot), normalized to the non-inhibited calcium current. A somatic spike was detected when its amplitude reached a threshold of 80 mV.

4.4.3 Synaptic plasticity and pairing protocol

Synaptic plasticity was implemented with an additive spike-timing dependent plasticity rule as in (Song et al., 2000):

$$\Delta w = \begin{cases} -A_- \exp(\frac{\Delta t}{\tau_-}) & \text{if } \Delta t \leq 0 \\ A_+ \exp(-\frac{\Delta t}{\tau_+}) & \text{if } \Delta t > 0 \end{cases}$$

where Δt is the difference between pre- and postsynaptic spike time: t_{post} - t_{pre}. A postsynaptic spike was counted when the membrane voltage at the synapse reached a threshold of -20 mV. For apical tuft plasticity, a postsynaptic spike was counted when the calcium concentration reached a threshold of 0.5 mM. We used a different model for distal plasticity, assuming that the calcium spike governs calcium dynamics and thus plasticity in the distal dendrite (for an illustration of our argument, see S5 Fig). Parameters were: potentiation factor A_+ = 0.001, depression factor A_- = 0.00106, potentiation time constant τ_+ and depression time constant τ_- were both 20 ms. Hard bounds set to 0 and 0.0001 µS were imposed on synaptic weights.

Somatic current injection was paired with dendritic synapse activation 100 times with a frequency of 1 Hz with varying Δt.

4.4.4 Circuit model

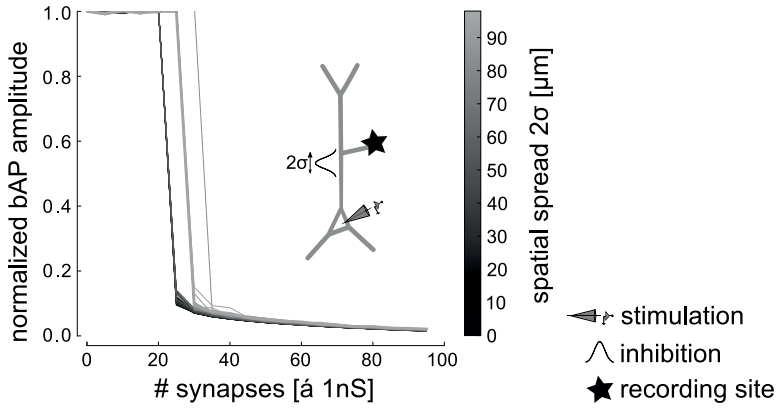
The feedforward inhibitory circuit contained the introduced multi-compartmental pyramidal neuron model and a model of a fast-spiking interneuron (IN). The latter, a single-compartment model with Hodgkin-Huxley-type sodium and potassium conductances, was taken from (Destexhe et al., 1998) (ModelDB accession: 3817). The interneuron with slower spike initiation was adapted from the fast-spiking interneuron by changing the sodium dynamics. The opening rate α was changed by a factor of 0.1, the closing rate β by a factor of 0.2. Both, the interneuron and the pyramidal neuron received EPSPs (NEURON Exp2Syn with rise and decay time constants of 0.5 ms and 2 ms, respectively, and a reversal potential of 0 mV) from an excitatory source (EX) at time t_0. The excitatory synapse onto the interneuron had a maximum conductance of 300 nS. To mimic inputs from oblique dendrites, eight synapses were distributed onto the apical trunk of the pyramidal neuron between 140 and 420 µm (Megias et al., 2001) with a total maximum conductance of 20 nS. The inhibitory synapse from the fast-spiking interneuron had the same properties as all shunting synapses modeled in this study (τ_{rise}=0.5 ms; τ_{decay}=5 ms; reversal potential -73 mV).

4.4.5 Detailed L5 model

From (Hay et al., 2011), we took the neocortical L5 pyramidal cell model constrained by both BAC firing and perisomatic step current firing with an anatomically reconstructed morphology (ModelDB accession: 139653). We did not change any parameters. To investigate the all-or-none effect, the model was stimulated with somatic current injection as in (Hay et al., 2011). We added inhibitory synapses (NEURON Exp2Syn synapses; rise and decay time constants 0.5 and 5 ms, respectively) to the model and placed them ~100 µm (proximal) and ~617 µm (distal) from the soma. The onset of inhibition was 2.5 ms after the onset of the somatic pulse if not varied. Voltage traces were measured in the soma, the oblique branch and an apical tuft branch. In Fig. 4.5E and F, inhibition had maximum conductances of 100 nS (proximal) and 200 nS (distal).

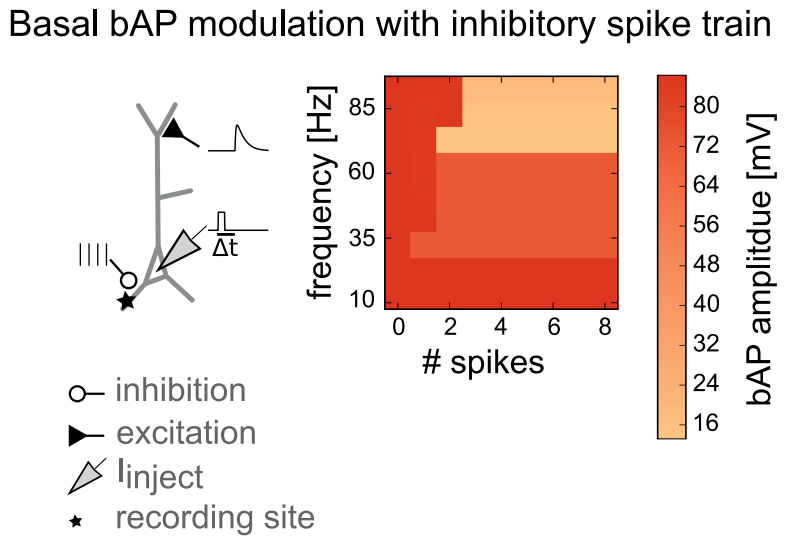
4.5 Supporting Information

S1 Fig



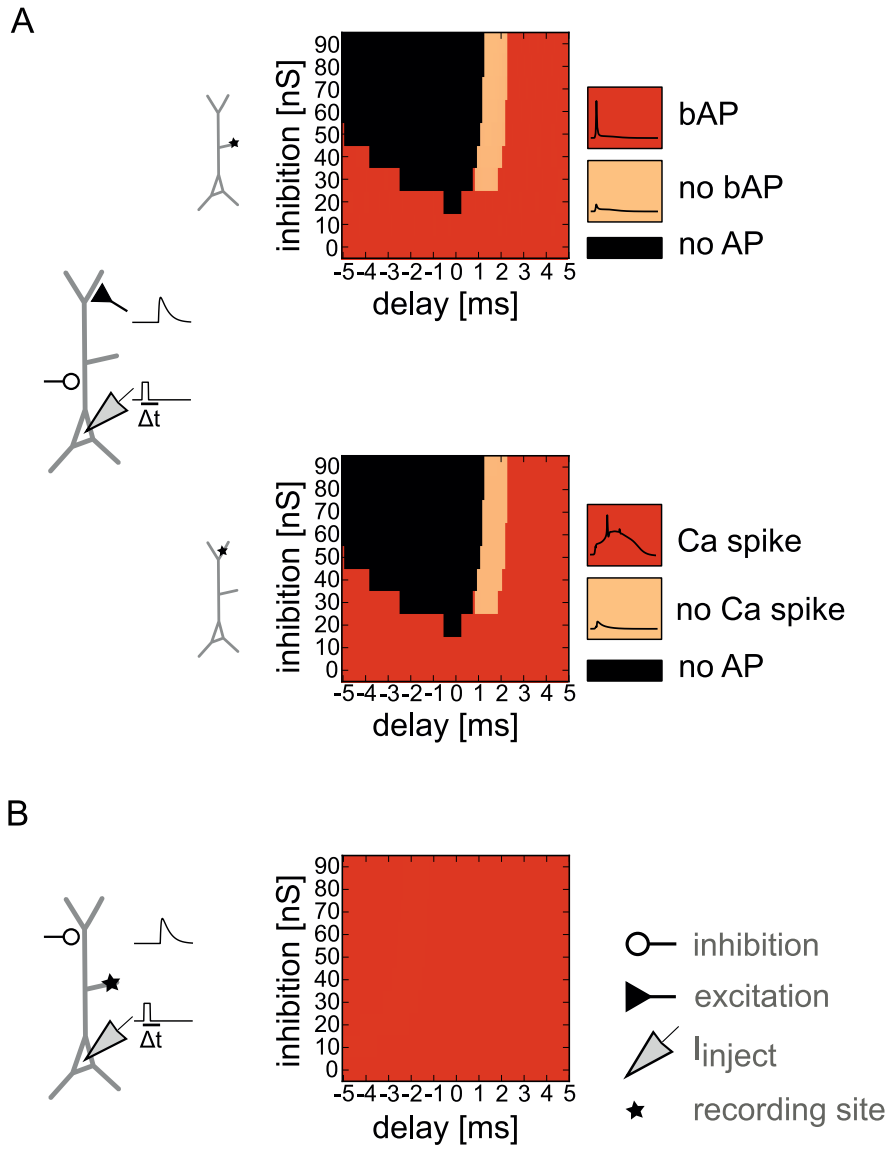
Spatial spread of inhibition. Inhibitory synapses were normally distributed around a mean of 90 µm from the soma with varying standard deviation σ up to 50 µm. The effect on the normalized bAP amplitude is shown as a function of the number of inhibitory synapses, each with a maximum conductance of 1 nS.

S2 Fig



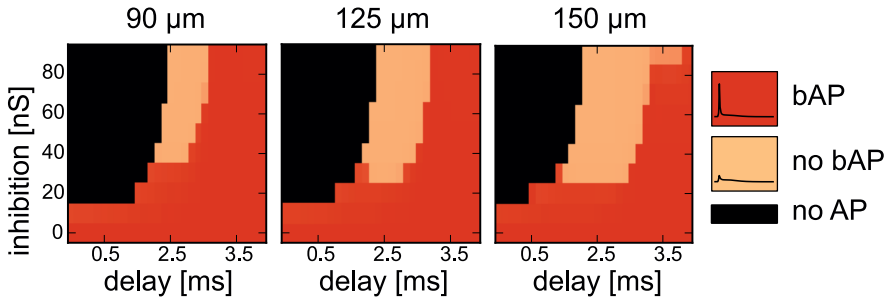
Basal modulation in the presence of a calcium spike. Modulation of bAPs propagating into the basal dendrite when a calcium spike was triggered by concurrent somatic current injection and dendritic excitation (with a delay Δt of 0 ms, as in Fig. 4.4A). Shown (color-code) is the maximum bAP amplitude measured in the basal dendrite 75 µm from the soma as a function of basal inhibition. The number of spikes in the inhibitory spike train vary along the horizontal axis, the frequency with which the inhibitory neuron fired varies along the vertical axis. Higher frequencies than 75 Hz (chosen in Fig. 4.4A) were also sufficient to inhibit the train of bAPs with the same amount of synaptic discharges. However, generally holds that with higher frequency more synaptic discharges are needed to cover the duration of the burst.

S3 Fig



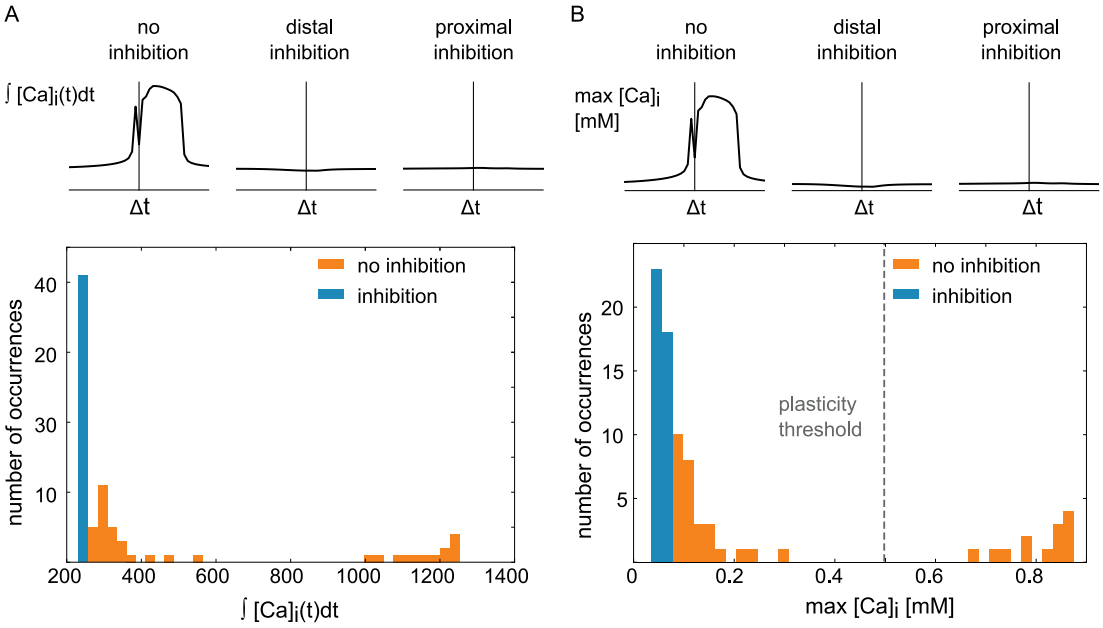
Timing requirements - additional plots. Results are in the same format as in Fig. 4.3B/C (color-code and axes are the same). A: Proximal inhibition on the apical dendrite and its effect on bAPs (top) and calcium spikes (bottom), when the neuron was stimulated by somatic current injection and dendritic excitation (with a delay Δt of 0 ms). When proximal inhibition abolished the bAP, it also affected the generation of a calcium spike. B: Distal inhibition on the apical dendrite did not affect bAPs in the oblique dendrite.

S4 Fig



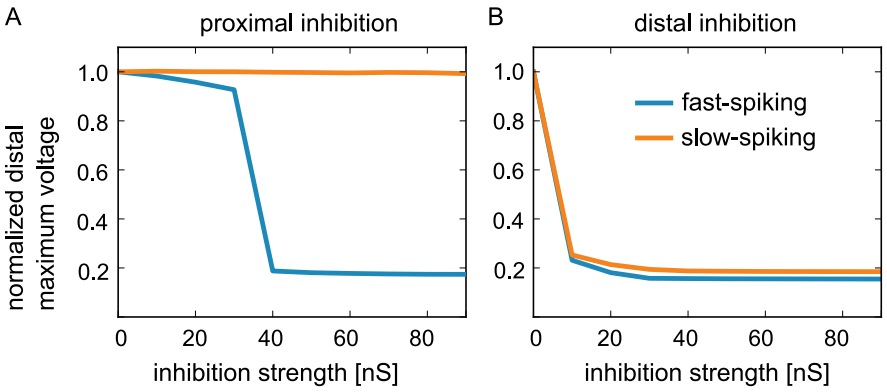
Width of the timing window as a function of inhibitory location. Timing requirements for bAP modulation as a function of the dendritic location of inhibition. The simulation paradigm is identical to that in Fig. 4.3C (dendritic stimulation). Color-coded is the amplitude of the bAP measured in the oblique dendrite as a function of the strength and timing of proximal inhibition. Unless somatic spiking was inhibited (black), either a full-blown bAP (red) or no bAP (light orange) could be observed. Location of inhibition was varied; distance to soma increases from left to right, as marked. All other parameters as in Fig. 4.3C. The width of the modulation window (light orange area) increased with distance of the inhibitory synapse from the soma and exceeded 1 ms for locations more distal than or equal to 150 µm.

S5 Fig



The distribution of distal calcium concentration is bimodal. BAC firing and the corresponding distal calcium influx is triggered if pre- and postsynaptic spike times are coincident. Therefore, the amount of calcium, quantified by the time integral of the distal calcium concentration (A) or its maximum amplitude (B), is dependent on the time difference Δt (top panel in A and B, Δt varies between -20 and 20 ms). Because the calcium spike is a nonlinear event, the amount of calcium is bimodally distributed (bottom panel in A and B), such that BAC firing governs calcium dynamics in the distal dendrite. Therefore, a threshold for plasticity based on the calcium concentration could be easily set by locating it in-between the peaks of the distribution (dashed line in B bottom). In the presence of (proximal or distal) inhibition, the amount of calcium was low, regardless of Δt, because BAC firing was prevented (top middle and right in A and B, bottom panel in A and B). For both proximal and distal inhibition, the amount of calcium was below the chosen plasticity threshold (bottom in B).

S6 Fig



Example of the effect of inhibition onto the bAP amplitude for two different versions of an interneuron (with faster and slower dynamics, respectively). Both interneuron types were implemented in the feedforward circuit (see Fig. 4.7). The normalized maximum amplitude of the bAP in the distal dendrite was monitored as a function of the inhibition strength. A: Two interneuron types with different spike latencies were placed on the proximal dendrite (at 90 µm from the soma). The fast interneuron could eliminate the bAP when sufficiently strong, while the slower interneuron fired too late to have an impact onto the bAP. B: The same two interneuron types were placed on the distal dendrite (at 460 µm from the soma). Both interneurons were properly timed to inhibit the distal calcium spike. For further details see main text.

S1 Table

Table 4.1: **Parameters of the simplified morphology model.**

Parameter	Value	Parameter	Value
C_m	$0.75\,\mu F/cm^2$	s.$\bar{g}_{K,A}$	$0.029\,S/cm^2$
R_a	$150\,\Omega cm$	s.$\bar{g}_{Ca,H}$	$0.00030\,S/cm^2$
R_m	$40{,}000\,\Omega cm^2$	s.$\bar{g}_{K,Ca}$	$0.0005\,S/cm^2$
E_{leak}	-70 mV	d.$\bar{g}_{Ca,H}$	$0.00015\,S/cm^2$
E_{Na}	+60 mV	d.$\bar{g}_{K,Ca}$	$0.00025\,S/cm^2$
E_K	-80 mV	a.$\bar{g}_{Ca,H}$	$0.00045\,S/cm^2$
E_{Ca}	+140 mV	a.$\bar{g}_{K,Ca}$	$0.00025\,S/cm^2$
$\bar{g}_{Na}$	$0.009\,S/cm^2$	a.$\bar{g}_{Ca,L}$	$0.009\,S/cm^2$
$\bar{g}_K$	$0.01\,S/cm^2$	ax.$\bar{g}_{Na}$	$0.6\,S/cm^2$

s-soma, d-dendrite, a-apical calcium spike initiation zone, ax-axon. For $\bar{g}_{K,A}$, only the somatic value is given. But A-type potassium channels were present in all dendritic compartments, their density linearly increased 5-fold up to 500 µm from the soma. $\bar{g}_{Na}$ and $\bar{g}_K$ were uniformly distributed, only in the axon, $\bar{g}_{Na}$ had a different value.

5 Spike-timing dependent inhibitory plasticity to learn a selective gating of backpropagating action potentials

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Spike-timing dependent inhibitory plasticity to learn a selective gating of backpropagating action potentials

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Abstract

Inhibition is known to influence the forward-directed flow of neuronal information within neurons. However, also regulation of backward-directed signals, such as backpropagating action potentials (bAPs), can enrich the functional repertoire of local circuits. Inhibitory control of bAP spread, for example, can provide a switch for the plasticity of excitatory synapses. While such a mechanism is possible, it requires a precise timing of inhibition in order to annihilate bAPs without impairment of forward-directed excitatory information flow. Here, we propose a specific learning rule for inhibitory synapses to automatically generate the correct timing to gate bAPs in pyramidal cells when embedded in a local circuit of feedforward inhibition. Based on computational modeling of multi-compartmental neurons with physiological properties, we demonstrate that a learning rule with anti-Hebbian shape can establish the required temporal precision. In contrast to classical spike-timing dependent plasticity (STDP) of excitatory synapses, the proposed inhibitory learning mechanism does not necessarily require the definition of an upper bound of synaptic weights because of its tendency to self-terminate once annihilation of bAPs has been reached. Our study provides a functional context in which one of the many time-dependent learning rules that have been observed experimentally—specifically, a learning rule with anti-Hebbian shape—is assigned a relevant role for inhibitory synapses. Moreover, the described mechanism is compatible with an upregulation of excitatory plasticity by disinhibition.

5.1 Introduction

The forward-directed flow of information in neurons is regulated by inhibition (Lovett-Barron et al., 2012; Miles et al., 1996; Willadt et al., 2013). Inhibition can, for example, maintain mean neuronal firing rates in balanced networks (Isaacson and Scanziani, 2011; Moore et al., 2010), or constrain spiking to specific phases of a network rhythm (Bartos et al., 2007; Royer et al., 2012). Also the control of backward-directed information flow within neurons enlarges the repertoire of neural computations. This aspect, however, has been less extensively studied. Action potentials that backpropagate into the dendrite (bAPs), in particular, fulfill important functions. On the one hand, bAPs provide a necessary feedback signal for Hebbian forms of synaptic learning (Colbert, 2001; Markram, 1997): by informing dendritic synapses about postsynaptic somatic activity, they enable temporal coincidence detection between pre- and postsynaptic

spikes required for spike-timing dependent synaptic plasticity (Fuenzalida et al., 2010). An inhibition-gated control of bAPs may hence provide an acute switch for synaptic plasticity of excitatory synapses (Paulsen and Moser, 1998), thus implementing a mechanism for metaplasticity. On the other hand, successful propagation of bAPs from the soma to distal dendrites can in some neuron types—if coincident with dendritic depolarization—induce a calcium spike that leads to somatic burst-firing (BAC firing, described by Larkum et al. (1999b)). These dynamics have been assigned an important role for the association of different input streams (Larkum, 2013). Via gating of bAPs, inhibition (or disinhibition) may exert control over the availability of the burst-firing mode.

In this study, we analyze a generic mechanism by which dendritic inhibition can control the spread of bAPs in simplified CA1 and detailed L5 pyramidal neuron models. This mechanism has recently attracted attention because Müllner et al. (2015) showed in elegant experiments that precisely-timed inhibition can annihilate bAPs on their way to the distal dendrites. *Per se*, impairment or elimination of a regenerative dendritic signal via inhibition (Buzsáki et al., 1996; Tsubokawa and Ross, 1996) may seem straightforward. The challenge, however, lies in a simultaneous preservation of forward-directed excitatory information flow. Our recent computational work suggests that, if adequately timed, local dendritic inhibition can indeed successfully control the propagation of bAPs while maintaining excitatory orthodromic signal flow (Wilmes et al., 2016). This gating mechanism can be reliably implemented in a ubiquitous local circuit motif: feedforward inhibition. Despite seemingly ambitious requirements for temporal precision, physiologically-realistic delays between the parallel excitatory and inhibitory pathways in such a circuit are sufficient to selectively annihilate bAPs without silencing the postsynaptic neuron.

If the appropriate timing within the circuit is established, this effect is very robust. In this study, we focus on how the correct timing can be learned in the first place. To this end, we propose an inhibitory spike-timing dependent plasticity (iSTDP) learning rule that strengthens those inhibitory synapses that provide the right timing for bAP annihilation while weakening inhibition from other inhibitory synapses. The learning rule exhibits interesting features: (1) it has an anti-Hebbian shape and (2) it exhibits self-termination. The rule leads to local circuits with appropriate timing for a stable control of bAPs and hence can help to establish a switch of excitatory plasticity and the regulation of BAC firing via inhibition and disinhibition. Beyond the control of bAPs, our study assigns a new functional role to previously observed anti-Hebbian learning rules.

5.2 Methods

Simulations were performed in NEURON (Hines and Carnevale, 1997), with an integration time step of 0.1 ms (0.025 ms for Fig. 5.1B and Fig. 5.2) at a temperature of 30°C. The simulation code will be made available at the ModelDB database (http://senselab.med.yale.edu/ModelDB/).

Morphology and physiology of the postsynaptic neuron model

The ball-and-stick neuron model (Figure 5.1A) consisted of a soma (diameter and height 18.5 µm, nseg=1) and a dendrite of 500 µm (diameter 2 µm, nseg=201). An additional dendritic compartment was added to prevent boundary effects, not shown in the schematic figures. The passive parameters of the neuron were: membrane capacitance C_m=0.75 µF/cm^2, axial resistivity R_a=150 Ω cm, membrane resistance R_m=40,000 Ω cm^2, and leak reversal potential E_L=-70 mV. Soma and dendrite hosted active conductances to allow for (backpropagating) action potentials. Inactivating sodium and delayed-rectifying potassium conductances with channel kinetics from Migliore et al. (1999) (ModelDB accession 2796) were distributed with uniform density (Magee and Johnston, 1995) such that bAPs propagated within the dendritic tree. A-type potassium channels (Migliore et al., 1999, ModelDB accession 2796, kaprox.mod) were added to account for the attenuation of the bAP (Hoffman et al., 1997), with linearly increasing density from soma to the distal dendrite. The conductances of all channels and the spatial distribution of the A-type potassium channels were fitted such that the model reproduced the experimentally observed bAP attenuation in CA1 pyramidal cells (Spruston et al., 1995). Dendritic sodium and delayed-rectifying potassium channels were distributed uniformly with a maximum conductance of 0.009 S/cm^2 and 0.01 S/cm^2, respectively. The voltage dependence of dendritic sodium channel activation was shifted by +5 mV to allow apical excitatory postsynaptic potentials (EPSPs) to cause somatic spikes without eliciting dendritic spikes. The reversal potentials were: E_{Na}=+60 mV and E_K=-80 mV. The A-type potassium peak conductance increased five-fold up to 500 µm from the soma with an initial value of 0.029 S/cm^2. The axon initial segment consisted of only a single compartment with increased sodium channel density compared to dendritic compartments (0.6 S/cm^2 in total), matching the order of magnitude of the experimentally measured value (2,500 pS/µm^2=0.25 S/cm^2) based on modern sodium imaging techniques (Kole et al., 2008). Voltage dependencies were shifted in 50% of the axonal sodium channels by -10 mV in order to ensure that the action potential is initiated in the axon initial segment. Shifted voltage dependencies of sodium channels in the axon initial segment have been experimentally observed (Colbert and Pan, 2002; Fleidervish et al., 2010; Hu et al., 2009; Turner et al., 1991).

5.2.1 bAP propagation and inhibition

To induce a bAP, the ball-and-stick model was somatically stimulated with a step current injection of 4 ms duration and 0.2 nA amplitude. The bAP was monitored along the dendrite. One inhibitory synapse was placed 200 µm from the soma, at maximum conductances of 0 nS, 30 nS and 100 nS, respectively. When both, timing and strength of inhibition were varied, the amplitude of the bAP in the distal dendrite (450 µm from the soma) was measured and normalized to its uninhibited value. A somatic AP was defined to occur if the somatic membrane potential reached an amplitude of 80 mV, measured from the resting potential (~-74 mV). For those timings and weights of inhibition for which the somatic AP was below this threshold value, Fig. 5.1B is dark gray.

5.2.2 Circuit

The feedforward inhibitory circuit is intended to study basic principles of the mechanism based on excitation-inhibition timing. The circuit was hence kept relatively simple and contained the ball-and-stick (postsynaptic) neuron model (described above) and a model of a fast-spiking interneuron (IN). The latter, a single-compartment model with Hodgkin-Huxley-type sodium and potassium conductances, was taken from Destexhe et al. (1998) (ModelDB accession: 3817). Both, the interneuron and the postsynaptic neuron received EPSPs from an excitatory source (EX) at the same time. During a pairing protocol, the circuit was repeatedly stimulated with a stimulation frequency of e.g. 10 Hz in Fig. 5.2.

Excitatory and inhibitory synapses

All synapses were modeled as time-dependent conductance changes. The postsynaptic neuron was excited by eight relatively strong excitatory synapses distributed equally between 150 µm and 412.5 µm over the (apical) dendrite as an approximation of inputs from eight oblique dendrites (NEURON Exp2Syn with rise and decay time constants of 0.5 ms and 2 ms, respectively, and a reversal potential of 0 mV). The total maximum conductance of these synapses amounted to 20 nS. The excitatory synapse onto the interneuron had a maximum conductance of 200 nS. Upon input from the excitatory source, both the postsynaptic pyramidal neuron and the interneuron elicited one spike. 100 plastic inhibitory synapses from the interneuron to the postsynaptic neuron were placed on the proximal dendrite of the postsynaptic neuron and initiated with small maximum conductances of 0.001 nS. We chose 100 inhibitory synapses to have a representative sample for the range of possible timings. The inhibitory synapses had a double-exponential time course (NEURON Exp2Syn synapse; rise and decay time constants 0.5 and 5 ms, respectively). Inhibition had a shunting effect with a reversal potential close to rest, i.e. -74 mV. Each of the 100 inhibitory synapses in the inhibitory pathway had a different mean delay from the spike time in the inhibitory interneuron to the onset of the synaptic conductance change. The means of these synaptic delays were equally distributed according to a uniform distribution in [1,11] ms. The synaptic delays jittered around their mean with each pairing, such that each delay was distributed around its mean according to a Gaussian distribution with a standard deviation of 0.5 ms. For the inset to Fig. 5.2C, inhibitory synapses were distributed on the dendrite according to a uniform distribution in the region [100,300] µm from the soma.

Inhibitory synaptic plasticity

The anti-Hebbian learning rule for inhibitory synaptic plasticity was the reversed and shifted version of the simple additive spike-timing dependent plasticity rule (Song et al., 2000):

$$\Delta w = \begin{cases} A_+ \exp(\frac{\Delta t - d}{\tau_+}) & \text{if } \Delta t \leq d \\ -A_- \exp(-\frac{\Delta t - d}{\tau_-}) & \text{if } \Delta t > d \end{cases} \tag{5.1}$$

where Δt is the difference between pre- and postsynaptic spike time: t_{post} - t_{pre}. The onset of the inhibitory conductance t_{inh} was taken as the presynaptic spike time. A

postsynaptic spike was counted when the membrane voltage at the synapse reached a threshold of -40 mV. Parameters were: potentiation factor A_+ = 0.1 nS, depression factor A_- = 0.1 nS, potentiation time constant τ_+ and depression time constant τ_- were both 10 ms. Weights were constrained to be positive.

In addition, we also explored a learning rule related to the anti-Hebbian rule that approximates the schematic rule (introduced in Results and the Appendix). The related rule was obtained from the anti-Hebbian shape by cutting the potentiation domain at 0.02 ms, such that synapses with a $\Delta t < 0.02$ ms were neither potentiated nor depressed. We normalized the depression domain such that the total integral of the iSTDP window equaled 0. See Appendix for the schematic rule.

5.2.3 Voltage recordings and synaptic weights

To measure the amplitude of the somatic AP and bAPs during pairings, we first cut out the spikes in the interval [-10,10] ms around the time point of stimulation and then took the peak (maximum amplitude) of each. The synaptic weight was monitored over the time course of the simulation. In Fig. 5.2D, we plotted the weights as follows: we first subtracted the initial synaptic weight of each weight value and then divided the result by the initial synaptic weight, to plot how much each synaptic weight changed relative to its initial value. The number of pairings is indicated on the x-axis. The amplitudes of the somatic AP and the bAPs at the end of the pairing protocol were measured to quantify the success of the learning rule in Figures 5.4C and 5.5A.

5.2.4 Disinhibition

The circuit was initialized with learned synaptic weights such that the appropriate timing of inhibition was provided (i.e. after stimulation as in Fig. 5.2 with inhibition at 200 µm from the soma to learn the appropriate timing). Then, inhibitory synapses (at 200 µm) were turned off at random with different probabilities, varying between 0 and 1 in steps of 0.025. The amplitude of the bAP along the dendrite was monitored. To measure the plasticity threshold at different locations of inhibition, the circuit was trained with inhibitory synapses at three different locations (100, 150, 200 µm from the soma) and then disinhibited as before. The threshold for plasticity was measured as the amplitude of the largest bAP (measured at the site of inhibition) that did not recover. For each location, we measured the plasticity thresholds for 10 randomized trials, i.e., with different inhibitory synapses turned off, to obtain the distributions in Fig. 5.3B.

5.2.5 Detailed L5 model

The anatomically reconstructed neocortical L5 pyramidal cell model was taken from Hay et al. (2011) (ModelDB accession 139653, parameters as in the original study). The model cell was successively stimulated 100 times at a frequency of 5 Hz with somatic current injection with an amplitude as in Hay et al. (2011). We added 200 inhibitory synapses (NEURON Exp2Syn synapses; rise and decay time constants 0.5 and 5 ms, respectively) to the model and placed them ~150 µm from the soma. These synapses were plastic according to the same synaptic plasticity model used in the simple model.

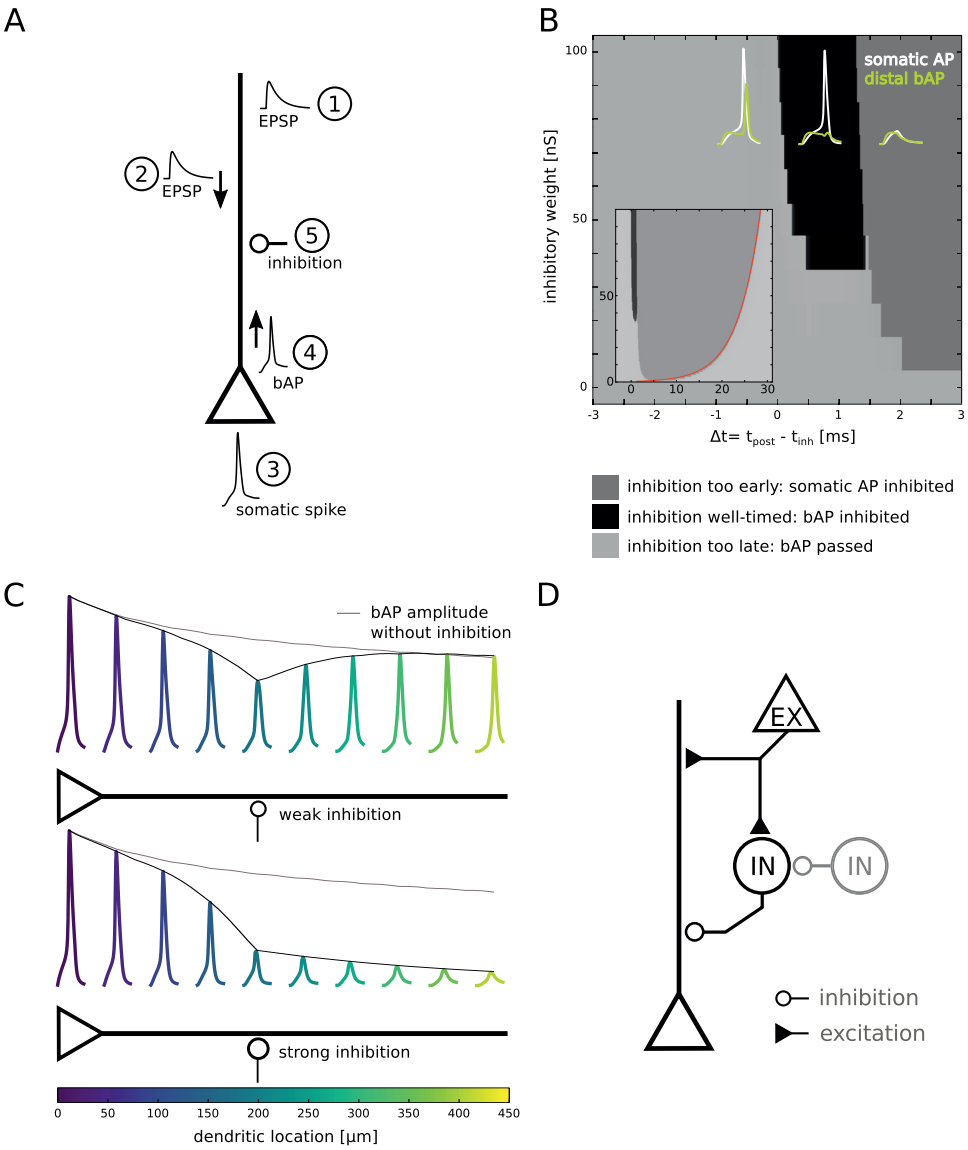

Figure 5.1: **Inhibition of the bAP.** (A) Illustration of the temporal sequence of events in the pyramidal neuron: (1) dendritic excitation, (2) electrotonic spread of the EPSP towards the soma, (3) generation of a somatic spike, (4) backpropagation of the AP into the dendrite, (5) inhibition gating the bAP. (B) Timing requirements for successful inhibition of the bAP. Depending on inhibition strength and timing relative to the bAP at the inhibitory synapse ($\Delta t = t_{post} - t_{inh}$), proximal dendritic inhibition either inhibited somatic AP initiation and *ipso facto* no bAP occurred (dark gray area), inhibited only backpropagation of the AP (black area), or did neither inhibit AP initiation nor AP backpropagation (light gray area). bAPs were assessed 450 µm from the soma. The inset zooms out to a larger range of timings. (C) bAP propagation along the dendrite in the presence of weak (30 nS) and strong (100 nS) proximal inhibition. Color encodes the distance from the soma. At the site of inhibition, the bAP amplitude was locally reduced. *Caption continued on the following page.*

Figure 5.1: The reduction had an all-or-none effect on further propagation: if inhibition was too small, the bAP recovered on its way towards the distal end (top); if inhibition was large enough, the bAP died out (bottom). For comparison, the amplitude of an uninhibited bAP is shown in gray. (D) Schematic of the feedforward inhibitory circuit (black). Synapses of the black interneuron (IN) onto the pyramidal cell are assumed to undergo iSTDP (100 synapses were later used to test the iSTDP rule). The gray interneuron (IN) controls excitability of the (black) feedforward inhibitory neuron and hence can exert control over bAPs in the pyramidal cell's dendrite. Stimulation of the excitatory cell (EX) was later used for pairing of spikes of the pyramidal cell and the black (IN) neuron.

The shift in the learning rule was d=2.5 ms. Voltage traces were measured in the soma and in a more distal branch as indicated in Fig. 5.5B (green spot).

5.3 Results

Fine-tuned regulation of the spread of bAPs into dendrites of pyramidal cells by inhibition constitutes a computationally beneficial mechanism. For such a mechanism to work, a millisecond-timing precision of inhibition relative to the excitatory postsynaptic potential (EPSP) and the somatic spike is essential (Müllner et al., 2015; Wilmes et al., 2016), which may at first glance seem ambitious. Here, we argue that the timing requirement can be met in an inhibitory feedforward circuit and suggest a spike-timing dependent learning rule for inhibitory synapses that automatically establishes a timing in the local circuit such that bAP propagation can be controled via inputs through these pathways.

5.3.1 The mechanism of inhibitory control

Before turning towards the inhibitory plasticity rule, we need to briefly review the scenario for bAP control (Wilmes et al., 2016). In a pyramidal neuron (whose bAPs are to be regulated) excitatory input from dendritic synapses in some distance to the soma causes an EPSP that propagates towards the soma and triggers a somatic action potential. This somatic spike then propagates back into the dendrites as a bAP (Fig. 5.1A), where dendritic inhibition placed along the path can hinder its further propagation (Koch et al., 1983). The timing of the inhibitory input is hence constrained: (1) it should arrive late enough to allow for the EPSP to pass and trigger the somatic action potential and (2) it should arrive early enough to interact with and weaken the passing bAP. A temporal window of approximately 1 ms width has been shown to meet both requirements (Wilmes et al., 2016), see also Fig. 5.1B. Interestingly, inhibition affects the bAP in an all-or-none manner due to the regenerative nature of the active bAP. While the effect of inhibition on voltage at the site of inhibition is gradual, the bAP on its further way either recovers to its original strength or dies out (Fig. 5.1C). From the perspective of dendritic locations more distal than the site of inhibition, inhibition can thus achieve a binary switch of the bAP and, consequently, a binary switch of further processes that would have been initiated by the bAP (such as plasticity of excitatory synapses or BAC firing).

The required timing constraints can be met in a circuit of feedforward inhibition (Fig. 5.1D): excitation directly stimulates the pyramidal cell as well as a parallel inhibitory pathway (Fig. 5.1D, black interneuron), which projects to the pyramidal dendritic location where bAPs are to be controled. Such a network design also conveniently opens up the possibility to, in turn, control the inhibitory interneuron via another inhibitory cell (Fig. 5.1D, gray inhibitory cell), which effectively switches the interneuron on and off and hence also exerts direct control over the propagation of the bAP in the pyramidal cell.

5.3.2 The inhibitory STDP rule

While such a hard-wired circuit seems very useful for the described mechanism of bAP control in pyramidal cells, the scenario relies on a correct delay between the pyramidal excitation (i.e. its somatic spike) and the onset of inhibition. This delay, however, depends on many parameters, including local signal integration times, the speed of propagation of EPSPs and bAPs, dynamics of spike generation in both the pyramidal and the inhibitory cell, or neuromodulation, to name a few. In this study, we hence propose a learning rule for the inhibitory synapses (onto the pyramidal cell) that helps to select circuits with the appropriate delay between excitation and inhibition. In the following, we specifically show that an inhibitory STDP rule (based on the spike-time difference between the presynaptic inhibitory cell and the postsynaptic pyramidal neuron) with anti-Hebbian shape qualifies to fine-tune the delay, enabling an efficient control over pyramidal bAPs. On the technical side, please note that we define t_{post} as the time point when the bAP crosses a voltage threshold at the synapse and t_{pre} as the inhibitory conductance onset in the pyramidal dendrite. To indicate the inhibitory nature, we also refer to t_{inh} where appropriate, which equals t_{pre}.

We can infer the required iSTDP rule from our knowledge about the effective time windows of inhibition (Fig. 5.1B): The rule should favor synapses that activate shortly before the bAP arrives at the inhibitory site (and hence cancel the bAP), but punish synapses that activate several milliseconds before the somatic AP is initiated (and hence impair EPSP-mediated AP initiation). Those synapses that activate too late to affect any of the two signals can remain unaltered (in particular, if their weight is small), because they do not interfere with the mechanism. In principle, they could also be depressed. A corresponding iSTDP window is schematized in Fig. 5.2A top (see also Appendix). Note that in the following we will refer to this rule as the *schematic* rule. Interestingly, the seemingly tight time window of potentiation is not essential; more biologically plausible iSTDP rules can successfully strengthen inhibitory synapses such that the bAP is canceled if two requirements are fulfilled: (1) synapses with small positive temporal differences between inhibition onset and arrival of the bAP at the synapse are fostered, and (2) synapses with large positive temporal differences are punished. One such iSTDP rule has an anti-Hebbian shape with a small shift d of ~1.5 ms in the direction of *pre-before-post* timing (i.e. towards the right in Fig. 5.2A bottom), corresponding to positive values of Δt between t_{pre} and t_{post}. All results presented in the following are based on this anti-Hebbian learning rule. They qualitatively also hold for two other rules explored (unless otherwise indicated): the above mentioned schematic rule as well as a modified version of the anti-Hebbian rule meant to approximate the schematic

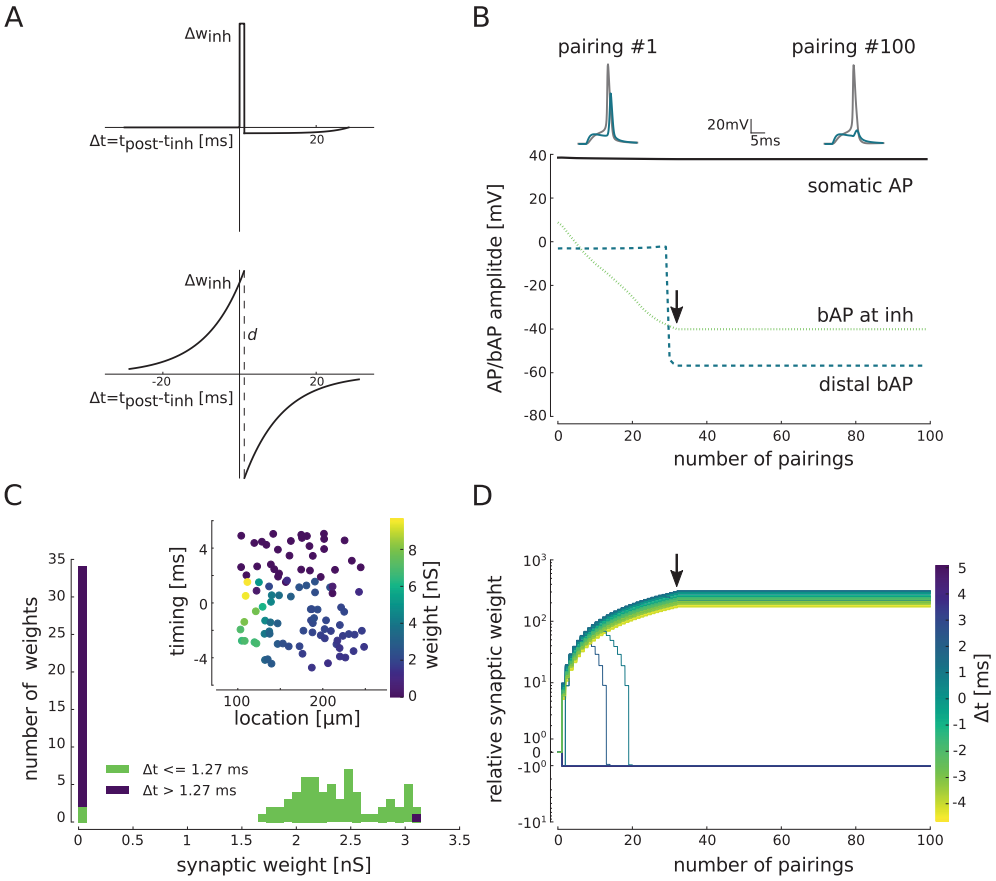

Figure 5.2: **Learning precisely timed inhibition with the anti-Hebbian iSTDP rule.** (A) The inhibitory STDP rules. The synaptic weight change Δw_{inh} (for each pairing) is a function of the temporal difference Δt between the time of the onset of the inhibitory conductance (t_{inh}) and the time when the bAP crosses threshold at the synapse (t_{post}). Top: the schematic rule. Bottom: the anti-Hebbian STDP rule with a small positive shift d=1.27 ms. (B) Amplitudes of somatic AP, bAP at the site of inhibition (200 µm), and bAP at a distal location (450 µm) as a function of the number of pairings. The somatic spike stayed intact; bAP amplitude at the inhibitory site decreased gradually, until it crossed the plasticity threshold and remained constant; bAP amplitude at the distal cite changed abruptly (all-or-none effect). Top: Two example traces of the somatic spike (gray) and the distal bAP (blue) at pairings #1 and #100. (C) Final weight distribution (at pairing #100; after learning self-terminated); color-code indicates the timing group Δt of individual synapses (smaller or equal, or larger than d). Inset: weight distribution at pairing #100 for synapses distributed in space between 100 µm and 300 µm (D) Evolution of inhibitory synaptic weights during learning. Weights are plotted relative to their initial value (before learning). Color encodes the synapse-specific timing Δt. Inhibitory synapses with $\Delta t > d$ were depressed, the others potentiated. Updates of the weights terminated once bAP amplitude fell below the plasticity threshold (marked by the arrow, see also corresponding arrow in panel B).

rule. For the latter rule, weights did not change for $t_{post} \leq t_{pre}$, while weight changes were identical to the anti-Hebbian rule for $t_{post} > t_{pre}$.

5.3.3 Effect of the inhibitory learning rule on the bAP

Based on the described learning rules, we next demonstrate that the proposed mechanism of inhibitory spike-timing dependent plasticity indeed selectively strengthens inhibitory neurons with the appropriate timing in a circuit of feedforward inhibition. We considered 100 inhibitory synapses, each with a different mean synaptic delay.

Initially, all inhibitory synapses were weak and hence did interfere neither with passive propagation of the excitatory input to the soma, nor with the initiation of a somatic spike, nor with the backpropagation of the action potential (Fig. 5.2B). We induced inhibitory synaptic plasticity by evoking postsynaptic pyramidal and presynaptic inhibitory activity via stimulation of the upstream excitatory neuron, resulting in pairings of single postsynaptic pyramidal spikes with single spikes in the inhibitory neurons. All inhibitory synapses were plastic according to the anti-Hebbian learning rule (Fig. 5.2A). Similarly to STDP mechanisms of excitatory synapses, we assume that, locally, the bAP informs the synapses about postsynaptic spiking and, hence, about the relation of t_{pre} to t_{post}. Technically, the plasticity mechanism employed here requires a threshold value for a bAP amplitude to be considered as sufficiently large to serve as a valid reference signal reflecting t_{post}. At the site of inhibition, a threshold of -40 mV was hence assumed for detection of a bAP. In the following, we refer to this threshold as the threshold for (inhibitory) plasticity, because in absence of a bAP no weight changes of the synapses were induced.

As expected, the amplitude of the bAP at the site of inhibition was gradually reduced with each pairing (Fig. 5.2B bottom, dotted line). This process continued until the local bAP amplitude was decreased below the bAP detection threshold of -40 mV (corresponding to the plasticity threshold; i.e. no further synaptic weight changes were initiated), see also arrow in Fig. 5.2B. Accordingly, synaptic weights first increased and then remained constant once the bAP was too small to pass the plasticity threshold (Fig. 5.2D). This tendency to self-terminate is an interesting property of the inhibitory learning paradigm, see also Discussion.

In contrast, the effect of continued pairings on bAP amplitude at the distal site (Fig. 5.2B bottom, dashed line) was binary: Initially, the bAP fully recovered once the site of inhibition was passed (because inhibition was not yet effective enough). Once inhibition was strong enough (due to strengthening of more effective inhibitory synapses), the bAP amplitude suddenly decreased. The synaptic weights eventually converged to a bimodal distribution, where, indeed, synapses with the desired timing were potentiated, whereas those activating too early were depressed (Fig. 5.2C). Importantly, the somatic AP was not affected by inhibition at all (Fig. 5.2B bottom, solid line).

In addition, we note that both other learning rules also led to a successful annihilation of bAPs while preserving the somatic AP.

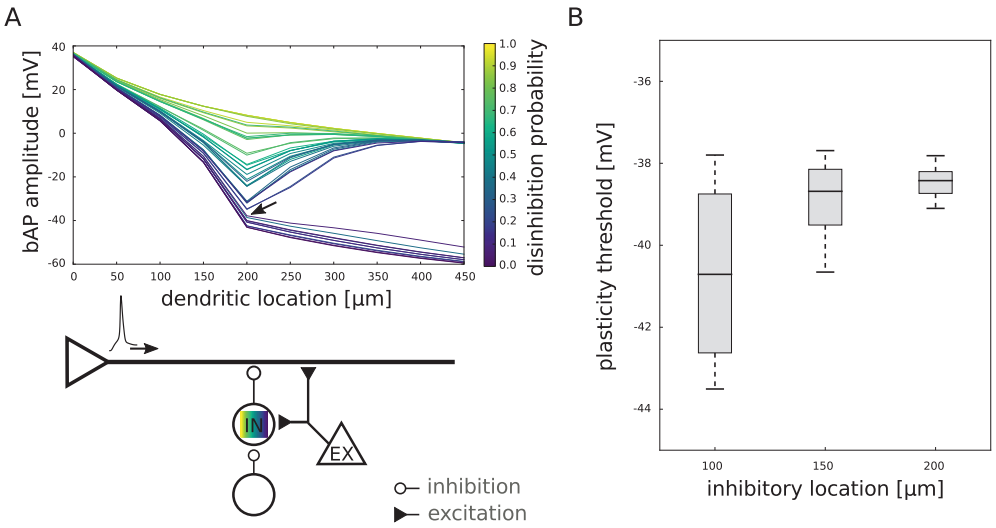

Figure 5.3: **Disinhibition can flexibly switch bAP cancelation on and off once the timing is established.** (A) Bottom: schematic of the circuit. The activation of the interneuron (bottom) disinhibits the pyramidal neuron by suppressing the feedforward inhibitory interneurons (IN). Top: Traces of bAP amplitude in the pyramidal dendrites as a function of location (from soma). For each trace, color encodes the percentage of feedforward interneurons (IN) that were silenced by the bottom interneuron. A maximal value for the plasticity threshold is given by the largest bAP amplitude at the site of inhibition that fails to recover (black arrow). (B) A distribution of maximal values for the plasticity threshold (as described in (A)), for each location of inhibition (from soma). Boxes represent the interquartile range (IQR) between first and third quartiles and the thick horizontal lines represent the medians. The whiskers denote the lowest and highest values within 1.5 x IQR from the first and third quartiles, respectively.

Switching inhibition

Once the timing of inhibition has been tuned by the iSTDP mechanism, bAPs are canceled by inhibition. This cancelation can be dynamically switched on and off on a very short timescale if an additional interneuron outside the feedforward circuit is considered (see Fig. 5.3A bottom). Silencing of the feedforward interneuron via this external interneuron automatically allowed bAPs in the pyramidal neuron to (again) invade the dendritic tree, as we show in Fig. 5.3A. This figure illustrates that the all-or-none nature of the effect of inhibition on bAP amplitude—resulting in a binary switch of the bAP amplitude for more distal dendritic locations—can also be observed if external interneurons modulate the activity of the (already tuned) feedforward inhibitory neuron. We note that from the perspective of iSTDP, this critical voltage value at the site of inhibition can serve as a reference for the plasticity threshold. Actually, in a given implementation, this critical voltage value (separating bAPs into recoveries or failures) constitutes an upper bound for the choice of plasticity threshold for which bAP suppression can be learned. On average, this critical value modestly increased the further the inhibitory synapse was located from the soma (Fig. 5.3B).

5.3.4 The shift in the learning rule

The shape of the learning rule determines the success of bAP suppression. While there is room for variation in the shape of the rule, one essential aspect is the transition from potentiation to depression at small positive Δt. Correspondingly, the anti-Hebbian window is sufficient, provided the horizontal shift in the *pre-before-post* direction is chosen appropriately. Fig. 5.4 illustrates two examples where the anti-Hebbian rule fails. If the horizontal shift is too large (Fig. 5.4A top), synapses with too early an inhibition are strengthened. In this case, the forward-directed excitatory signal flow is impaired and both pyramidal somatic spike and, consequently, the bAP fail (Fig. 5.4A bottom). If the shift is in the opposite direction (*post-before-pre*), see Fig. 5.4B top, bAP modulation fails because synapses with a timing that would annihilate the bAP are weakened; the bAP passes unhindered (Fig. 5.4B bottom). For inhibition at 200 µm distance from the soma, we found that the shift had to lie between 0.7 and 3.9 ms for the mechanism to work (Fig. 5.4C). The range of appropriate shifts slightly widened the further inhibition was located from the soma (Fig. 5.4D). These results were obtained for the anti-Hebbian learning rule.

5.3.5 Robustness of the mechanism

Adequate range of input frequencies: Embedded in a cortical network, pyramidal cells receive EPSPs at different frequencies, e.g. in the theta range in hippocampus (see e.g. Buzsáki et al., 1986). If the temporal sequence of EPSPs is too high, inhibition canceling bAPs may start interfering with the subsequent forward-directed EPSPs. The exact frequency above which forward signaling is affected, depends on EPSP propagation time (in particular between site of inhibition and soma) as well as on the time courses of IPSPs and EPSPs. For the parameter values used in this study (including rise and decay time constants of inhibition at 0.5 and 5 ms, respectively and a decay time constant of 10 ms for both potentiation and depression in the iSTDP learning rule), bAP modulation based on the anti-Hebbian learning rule was robust up to an excitatory input frequency of ~30 Hz (Fig. 5.5A). At frequencies above, inhibition interfered with the next forward-directed EPSP. The results were quantitatively similar for the other two rules tested.

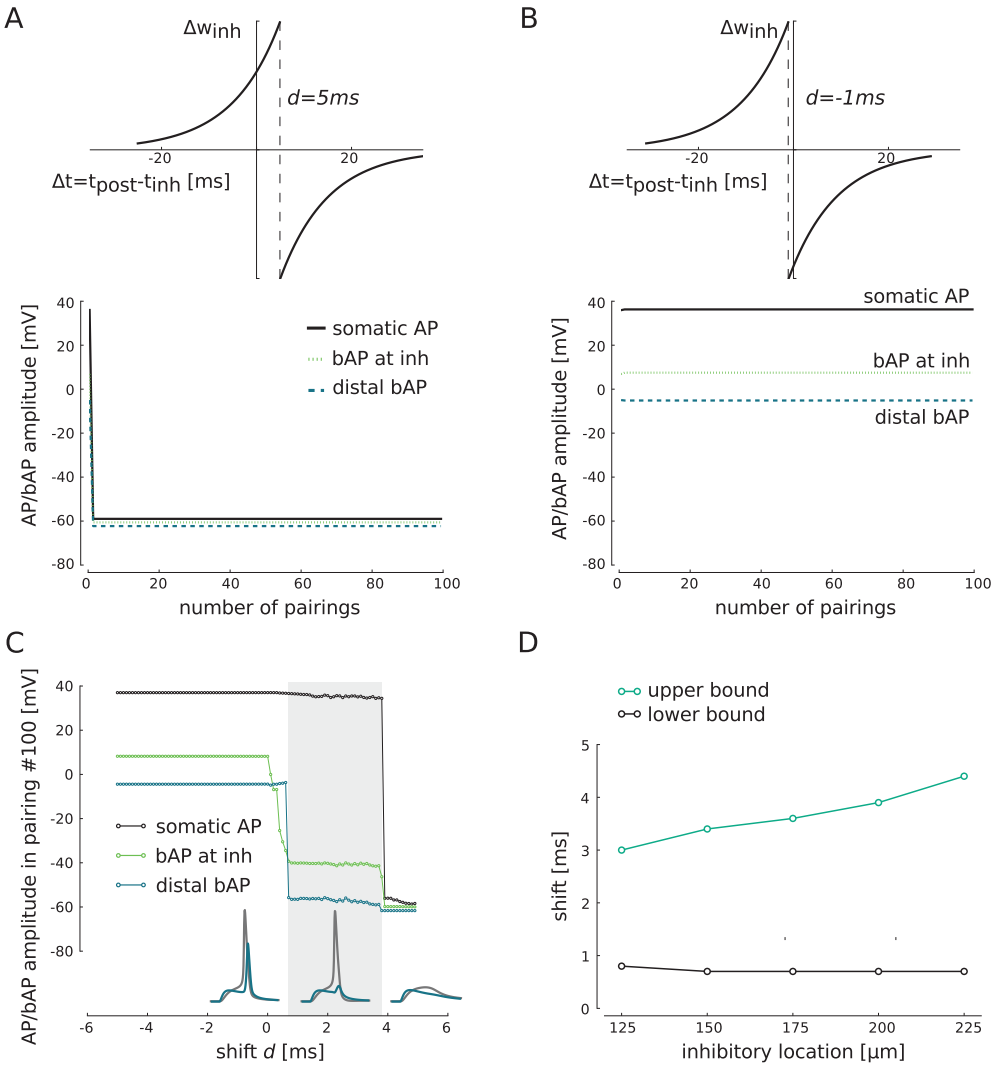

Figure 5.4: **Shifting the anti-Hebbian plasticity rule.** (A) Top: Example of the anti-Hebbian iSTDP rule shifted to larger, positive values, d=5 ms. Bottom: Amplitudes of pyramidal spikes (as indicated, compare Fig. 5.2B) as a function of pairings. Too early an onset of inhibition (as favored by this rule) interfered with the forward-directed EPSP propagation and impaired somatic spikes. Consequently, there were no bAPs. (B) Top: Example of the iSTDP rule shifted to smaller, negative values, d=-1 ms. Bottom: Too late an onset of inhibition (as favored by this value of d), did not "catch" the bAP and amplitudes of somatic spikes as well as bAPs were not affected by inhibition. (C) Systematic analysis of the effect of d. Amplitude of pyramidal spikes as a function of d after self-termination of learning (or pairing #100 in cases where the bAP was not annihilated). The range of d leading to successful cancelation of bAP without impairing the somatic spike is highlighted in gray. (D) Upper and lower bounds for d (as detected in (C)) as a function of the location of inhibition (from soma).

An anatomically detailed morphology: Furthermore, we confirmed that the mechanism (with an anti-Hebbian learning rule) also worked in a model with anatomically reconstructed morphology of a pyramidal cell. Inhibition learned to cancel the bAP after 28 pairings without effect on somatic spiking (Fig. 5.5B).

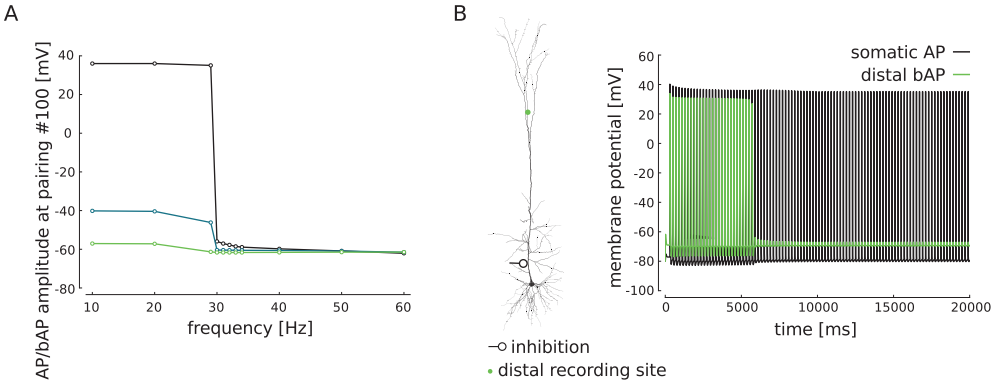

Figure 5.5: **Robustness of the mechanism.** (A) Adequate range of input frequencies: Amplitudes of pyramidal spikes (as marked, compare Fig. 5.2B) after learning (pairing #100) with anti-Hebbian iSTDP as a function of stimulation frequency (i.e. the frequency of distinct activation events of the external excitatory neuron (EX), see Fig. 5.1D). The bAP suppression mechanism was robust for input frequencies up to several tens of Hz, but broke down above 30 Hz because inhibition interfered with the next pyramidal EPSP event. (B) Results hold in an anatomically detailed pyramidal model: Example voltage traces illustrating that inhibition likewise suppressed bAP propagation in this model. Left: morphology; right: somatic APs (black) and distal bAPs (light green) as a function of time (locations of inhibition and recording as indicated left). Somatic APs were paired 100 times with inhibitory synaptic activations at a frequency of 5 Hz. After 28 pairings bAPs could be suppressed by inhibition while preserving somatic pyramidal spikes.

5.4 Discussion

In this study, we show that inhibitory STDP can fine-tune local circuits to inhibit retrograde dendritic signals in pyramidal cells while maintaining their feedforward-directed signaling. The learning rule analyzed here has an anti-Hebbian shape and constitutes a general mechanism to establish a precise timing that allows to regulate the propagation of bAPs. In contrast to classical, excitatory STDP paradigms, the proposed mechanism can terminate itself. Moreover, it can be switched on and off on short timescales via external interneurons that, exert control over the excitability of the inhibitory feedforward neurons. We show that, for physiologically realistic parameters, the mechanism is robust for stimulation frequencies up to several tens of Hz. Regulation of bAPs opens up interesting computational possibilities, including a fast switch of the plasticity of excitatory synapses.

5.4.1 Learning rules

In the context of this study, a competent learning rule strengthens inhibitory synapses that weaken the bAP, but punishes inhibitory synapses that impair the forward-directed EPSP. We find that a learning rule with anti-Hebbian characteristics as well as related inhibitory learning rules (specifically, the schematic rule in Fig. 5.2A top and the modified anti-Hebbian rule) can successfully establish a timing of inhibition appropriate to cancel the bAP without impairment of the EPSP-induced pyramidal spike. The crucial feature of these rules is a clear transition from potentiation to depression at the

time when inhibition starts to interfere with the forward-directed EPSP. We note that different rules are likely to differ in their efficiency in terms of the number of learning events (i.e. weight updates) required to learn to suppress the bAP as well as the number of strengthened inhibitory synapses at the end of the learning process (not explored here).

The proposed mechanism is robust if all synapses are initially weak, regardless of the specific shape of their distribution of weights. In the context of development, where the process of learning to suppress the bAP may be most relevant, it can be assumed that at the onset of this selection process many synapses are comparatively weak (Kano and Hashimoto, 2009; Kim and Kandler, 2003). The mechanism, however, requires that a bAP is initially present, because the bAP serves as the postsynaptic coincidence signal that is required for learning.

5.4.2 Self-termination of learning

An interesting property of the learning rule proposed here is its tendency to self-terminate. Classical STDP in excitatory synapses is inherently unstable with exploding weights, because synapses repeatedly undergoing causal *pre-before-post* pairings can grow without bound (Abbott and Nelson, 2000). Consequently, weight stabilizing mechanisms such as multiplicative and subtractive normalization (Abbott and Nelson, 2000; Miller and MacKay, 1994; Rubin et al., 2001) or modifications of the learning window (Babadi and Abbott, 2010) have been proposed. The proposed iSTDP mechanism for inhibitory synapses, in contrast, can lead to a stable weight distribution at the end of a learning sequence, because strengthened inhibitory weights *reduce* and eventually eliminate their own STDP coincidence signal. In contrast, excitatory synapses strengthen their coincidence signal, resulting in unbounded amplification. We consider this assumption reasonable for two reasons: First, inhibitory plasticity has been found to be spike-timing dependent (D'Amour and Froemke, 2015; Haas et al., 2006; Holmgren and Zilberter, 2001; Woodin et al., 2003), and bAPs seem to be the most likely candidate to inform dendritic synapses about postsynaptic somatic activity. Second, spike-timing dependent forms of inhibitory plasticity depend on calcium influx (Haas et al., 2006; Holmgren and Zilberter, 2001; Woodin et al., 2003), which is assumed to be mediated by bAPs.

In the model presented here, self-termination is expected if the inhibitory synapses are confined to a very small region of the dendrite (and differences in local bAP amplitude are negligible). If the spatial spread of inhibitory synapses is larger, however, it can happen that more distal synapses have learned to cancel the bAP, while the bAP amplitude at the more proximal synapses is still large enough for plasticity at these synapses to continue (further strengthening those synapses, as we note is the case in the inset to Fig. 5.2C where at pairing #100 the system has learned to suppress the bAP, but the weight distribution has not yet reached its steady state). Based on this observation, we hypothesize that the optimal postsynaptic coincidence signal for the inhibitory plasticity rule should not be the bAP amplitude itself, but rather a more spatially-averaged signal derived from local bAP amplitudes (like a calcium concentration).

5.4.3 One in a zoo of plasticity rules

The iSTDP rule described here is but one in the multitude of learning windows observed so far. For many of the learning rules discovered since the first description of spike-timing dependent plasticity (Bi and Poo, 1998) the functional role remains unclear. A particularly intriguing subgroup constitute learning rules for inhibitory plasticity in inhibitory-to-excitatory synapses. The large number of inhibitory neuron types (Klausberger, 2009) may suggest a large variety of learning rules. To this end, inhibitory plasticity has—similarly to excitatory plasticity—been found to depend on neuronal activity (Hartmann et al., 2008; Kilman et al., 2002; Kurotani et al., 2008; Maffei et al., 2006) and on the relative timing of pre- and postsynaptic spikes (D'Amour and Froemke, 2015; Haas et al., 2006; Holmgren and Zilberter, 2001; Woodin et al., 2003). Indeed, the plasticity rules measured so far (D'Amour and Froemke, 2015; Haas et al., 2006; Holmgren and Zilberter, 2001; Woodin et al., 2003) are very diverse and some have been assigned relevant functional roles in recent theoretical studies. For example, inhibitory plasticity has been shown to establish a balance of excitation and inhibition in networks (Luz and Shamir, 2012; Vogels et al., 2011), tune sensory systems to changing environments, alter the frequency selectivity of cortical neurons (Gilson et al., 2012), and stabilize network dynamics in general (Vogels et al., 2013). We expand this list: inhibition can learn to dynamically regulate learning or prevent the burst-like BAC firing mode, which supports the notion that inhibitory plasticity contributes to stable computations in the presence of dynamically changing conditions. While the rules discussed here differ from the few rules measured in inhibitory synapses, the anti-Hebbian rule resembles learning rules found in excitatory synapses of cerebellum-like structures (Bell et al., 1997; Han et al., 2000; Tzounopoulos et al., 2004) and in excitatory corticostriatal synapses (Fino et al., 2005).

5.4.4 Contribution to homeostasis

In this study, the iSTDP rule is assigned a putative functional role during brain development and contributes to the maintenance of homeostatic timing relations in the morphologically and physiologically changing conditions of the brain. During development, a process that establishes the timing to selectively control bAPs may be specifically important, in particular, as inhibition matures over early lifetime (Huang, 2009). The learning-driven selection process appropriately promotes and weakens synapses and hence may prune synapses according to the "use it or loose it" principle in the maturing brain. Moreover, the maintenance of a precise timing relation within a circuit poses challenges even in the adult brain, because morphological plasticity (such as activity-dependent myelination (Bakkum et al., 2008; Baraban et al., 2015) or activity-dependent interneuron firing delays (Dehorter et al., 2015)) persist beyond early developmental stages (Fields, 2005). Hard-wired circuits may not be optimally suited to adjust for changes affecting propagation times. In this context, it may be more relevant to rely on a learning rule with appropriate depression also for those synapses that activate too late relative to the bAP.

5.4.5 Frequency limits

Finally, being able to switch plasticity of distal (excitatory, pyramidal) synapses on and off by disinhibition offers an intervention point during learning (Letzkus et al., 2011). As a side remark, vasoactive intestinal polypeptide interneurons (known as VIP) may serve this role in the described circuit design (which has been identified in several neocortical areas, see Lee et al. (2013), Pfeffer et al. (2013), and Pi et al. (2013)). In this context, it is interesting that we have found the mechanism of bAP control to work up to several tens of Hz. Many established frequency bands fall into this regime and would hence be compatible with an inhibitory downregulation of learning via the proposed mechanism. For frequencies above, like those of higher gamma bands, the mechanism fails and one may speculate that during such episodes it should be switched off. This corresponds to an upregulation of learning (i.e. all bAPs pass) enabled by a disinhibition in the inhibitory feedforward circuit. Interestingly, gamma band activity and memory have been linked (Jensen et al., 2007).

5.4.6 Conclusion

This study combines a ubiquitous circuit motif with the interesting and recently debated mechanisms of inhibitory spike-timing dependent plasticity. The discussed learning rules facilitate a useful computation: the gating of backpropagating action potentials in pyramidal cells. In particular, it provides a homeostatic control for a precisely-timed inhibition in dendrites. While experiments involving several cells and thin dendritic processes are challenging, a computational approach allowed us to directly test the feasibility of such a mechanism in physiologically-constrained neuron models. Our analysis predicts a novel role for inhibitory plasticity that can be relevant for information processing and behavior, including mechanisms of metaplasticity.

5.5 Appendix: Derivation of the iSTDP rule

We derived an iSTDP rule from our computational analysis of the effects of timing and strength of inhibition on the initiation of the AP and the propagation of the bAP (Fig. 5.1B).

Potentiation domain

Fig. 5.1B shows that inhibition needs to fall into a narrow time window to inhibit the bAP (black area in Fig. 5.1B). The successful learning rule should potentiate those inhibitory synapses that are suited to inhibit the bAP, hence it should potentiate inhibitory synapses with a timing Δt that falls into this narrow time window. The boundaries of the time window depend on inhibition strength. To obtain safe boundaries for the rule, we chose strong inhibition of 100 nS as a reference. This ensures that synapses that can affect somatic AP initiation when strong are not potentiated. The *potentiation domain* of the plasticity rule hence spans Δt in the interval (0.02,1.27] ms (black area in Fig. 5.1B). All synapses falling into this interval are potentiated equally with an additive weight update $A^+ = 0.1$ nS.

Depression domain

The inset to Fig. 5.1B shows that inhibition starts to impair the initiation of a somatic AP for a range of timings (transition from light gray to dark gray). The effect of inhibition decreases with Δt: the larger the difference between inhibition onset and bAP (and hence AP), the stronger inhibition has to be to impair AP initiation. The successful learning rule should depress those inhibitory synapses that can impair AP initiation. The rule should depress inhibitory synapses proportional to their negative impact on AP initiation.

From simulations (Fig. 5.1B), we know for each synaptic strength, at which timing it starts to impair somatic firing, that is, we have data $D = \{(t^i, w^i), ..., (t^N, w^N)\}$. This critical weight-timing relation $w = f(t, c)$ is well described by the inhibitory decay time course $w = f(t, c) = \frac{c}{\exp\left(-\frac{t}{\tau_{\text{decay}}}\right) - \exp\left(-\frac{t}{\tau_{\text{rise}}}\right)}$, where $\tau_{\text{decay}} = 5$ ms and $\tau_{\text{rise}} = 0.5$ ms are the time constants of the inhibitory conductance, and c is a free parameter. The fit was obtained by minimizing $\arg\min_c \sum_{i=1}^{N} \left(w^i - f(t, c)\right)^2$ with the least squares method.

The depression domain of the STDP window is then defined by shifting the fitted curve $f(t, c)$ (red curve in Fig. 5.1B inset) by β along the y-axis to negative values $(-\beta + f(t, c))$, i.e. the more negative impact a synapse has, the more it will be depressed. The y-axis then reflects Δw. The depression window is limited by the potentiation window on the left, i.e. it starts at $\Delta t = 1.27$ ms (where the potentiation window ends). On the right, it is limited by where the downward shifted curve crosses 0, solving $-\beta + f(t, c) = 0$ for Δt with $\beta = 100$ nS. The solution is $\Delta t = 31.85$ ms (Fig. 5.2A top).

The schematic iSTDP rule

The final weight update for the schematic rule (Fig. 5.2A top) is given by

$$\Delta w = \begin{cases} A^+ & \text{if } 0.02\,\text{ms} < \Delta t < 1.27\,\text{ms}, \\ \alpha \left(-\beta + \frac{c}{\exp\left(-\frac{\Delta t}{\tau_{\text{decay}}}\right) - \exp\left(-\frac{\Delta t}{\tau_{\text{rise}}}\right)} \right) & \text{if } 1.27\,\text{ms} < \Delta t < 31.85\,\text{ms}, \\ 0 & \text{otherwise}, \end{cases}$$

where α is scaled such that the amount of depression equals the amount of potentiation, i.e. the integral of the full iSTDP learning window equals 0: with $c = 4.8\text{E-}4$ (result from least squares fit) and maximum potentiation $A^+ = 0.1\,\text{nS}$, the scaling factor for the depression window $\alpha = 4.8\text{E-}5$, such that maximum depression $A^- = \alpha * \beta = 4.8\text{E-}5 * 100\,\text{nS} = 0.0048\,\text{nS}$.

6 Discussion

6.1 Summary

The aim of this thesis was to study inhibition of dendritic signals with regard to the modulation of excitatory synaptic plasticity.

In the first part of the thesis (Wilmes, Sprekeler, and Schreiber 2016), we investigated how dendritic inhibition affects backpropagating action potentials (bAPs) and calcium spikes, the coincidence signals for plasticity.

1. We have shown that inhibition can control bAPs and calcium spikes in an all-or-none manner, enabling a binary switch of plasticity and the BAC firing mode. The switch of plasticity can be pathway-specific: the location of inhibition determines the dendritic compartments where dendritic signals are modulated.

2. We studied whether inhibition can cancel bAPs without interfering with the forward-directed information flow from dendritic excitatory synapses to the soma. In physiologically-constrained neuron models, we showed that with appropriately timed inhibition, EPSPs can trigger somatic action potentials even though the corresponding backpropagating signals are blocked. The required temporal precision for the annihilation of bAPs is very high (~1 ms). We demonstrated that this seemingly high precision can be provided by common feedforward inhibitory circuit motifs.

In the second part of the thesis (Wilmes, Schleimer, and Schreiber 2016), we addressed how feedforward inhibitory circuits can establish bAP control, given that inhibition timing needs to be precise, as shown in the first part.

3. We proposed a mechanism that allows to learn the appropriate strength and timing of inhibition, needed to exert control over backpropagating action potentials: a spike-timing dependent learning rule for inhibitory synapses. This rule ensures a tight onset of inhibition with respect to the postsynaptic action potential such that forward-directed EPSPs still pass. The proposed inhibitory learning mechanism has the potential to be self-limiting, as it terminates once inhibition cancels the bAP.

The two studies together demonstrate that an inhibitory switch of dendritic signals can serve as an effective mechanism that selectively regulates plasticity in functional circuits. Our results on the all-or-none modulation of bAPs and calcium spikes indicate that inhibition can indeed function as a switch of dendritic signaling and hence of both plasticity that depends on these signals, and the neural firing mode (BAC firing). We showed that the seemingly tight timing requirements for a selective gating of bAPs without impairing forward-directed information flow can be met in a realistic and

common feedforward circuit motif. This implies that plasticity can be controled on a large scale while maintaining stimulus selectivity and information processing capacities. Notably, feedforward circuit motifs, the presumable setting for the mechanism, can be found in almost any brain area (Tremblay et al., 2016). Hence, we provided a proof of principle that inhibition at a sweet spot on the dendrite is feasible to control plasticity of a large set of synapses. Yet, our results on the required tight timing raise the issue that modulatory inputs (such as inhibition) may need to be at least as precisely timed as the main processing inputs. Such an important role for timing in neural circuits has consequences for neural dynamics and their stability. With the second study, we tried to address this issue by suggesting that spike-timing dependent plasticity of inhibitory synapses (iSTDP) can select suitable inhibitory synapses and thereby establish an appropriately timed circuit. We demonstrated that such an iSTDP mechanism can in principle fulfill this role, but, as I will discuss later in this chapter, its robustness remains to be assessed under more realistic network conditions.

In light of recent findings, the described switch could be an essential ingredient of disinhibitory circuits that relieve principal neurons from inhibition. As such its investigation could bring us one step closer to understand how the brain regulates learning. In the following, I briefly mention the most important developments in related fields and then proceed to the general discussion.

6.2 The thesis in the context of recent research

During the last five years, many studies advanced our understanding of how inhibition might modulate plasticity: Disinhibitory circuits that can provide the essential switch of inhibition, as examined in this thesis, were discovered to be important for learning (1.). The consequences of dendritic inhibition on dendritic signals and synaptic plasticity were investigated experimentally (2.) and theoretically (3.).

1. **Disinhibitory circuits.** The mechanism of plasticity control via inhibition of dendritic signals, studied in this thesis, could operate in the recently discovered disinhibitory circuits that were shown to be involved in learning. Letzkus et al. (2011) found that during fear conditioning (with tones and mild electrical shocks), layer 1 interneurons inhibit PV cells in auditory cortex and, more importantly, that the resulting disinhibition of principal cells is necessary for successful fear learning. Soon after, disinhibitory circuits involving the inhibition of local interneurons, i.e. SOM and PV cells, were identified in further brain areas, such as somatosensory (Lee et al., 2013), and visual (Fu et al., 2014; Pfeffer et al., 2013) cortex, and shown to be neuromodulated by rewards and punishments (auditory cortex, Pi et al., 2013). Also, the influence of SOM and PV cells on principal neurons was studied in more detail in visual cortex (Atallah et al., 2012; El-Boustani et al., 2014; Lee et al., 2014; Wilson et al., 2012). Recently, disinhibition as a mechanism to enhance plasticity and learning could be observed during ocular dominance plasticity in visual cortex (Fu et al., 2015), and during fear conditioning in the amygdala (Wolff et al., 2014) and prefrontal cortex (Courtin et al., 2014). Together, these studies suggest that a (dis-)inhibitory dendritic switch of plasticity is of high behavioral importance. This in turn increases the relevance

and credibility of the dendritic mechanism studied in this thesis.

2. **Inhibition of dendritic signals in experiments.** First, Jiang et al. (2013) found that BAC firing is modulated by disinhibitory circuits, which suggests that it can indeed be switched on and off dependent on neuromodulatory state. This result is important in light of this thesis, because it provides a link between neuromodulation of disinhibitory circuits and inhibition of dendritic spikes, suggesting that these mechanisms play a role during neuromodulation of plasticity. Second, an important prerequisite for the mechanism of bAP control explored here is that a few inhibitory neurons can eliminate the bAP. Hence, our prediction for precisely timed bAP control became increasingly plausible in light of the experimental findings by Müllner et al. (2015), who showed that single inhibitory contacts can significantly reduce bAP-mediated calcium transients with high temporal precision. Finally, in support of the proposed pathway or compartment-specific plasticity processes, spine remodeling during learning was shown to be accompanied by compartment-specific adjustments of inhibitory synapses (Chen et al., 2015).

3. **Theory of dendritic inhibition.** Several theoretical studies explored the consequences of dendritic inhibition for dendritic signaling and plasticity: In contrast to a pathway-specific modulation as proposed here, Gidon and Segev (2012) showed that spatially distributed inhibitory synapses can control excitability (and hence plasticity) in dynamically changing dendritic zones, as dendritic inhibition has surprisingly non-local effects on dendritic excitability. Bar-Ilan et al. (2012) investigated how spatially distributed dendritic inhibitory synapses influence calcium transients, and hence plasticity. They found that interactions can happen at a high spatial resolution. This form of inhibitory plasticity control applies to calcium transients caused by excitatory postsynaptic potentials and differs from a modulation of more widespread dendritic signals for plasticity, as are backpropagating action potentials and calcium spikes. Both studies explored complementary dendritic inhibitory control processes that could occur in parallel to the ones investigated in this thesis.

Overall, these diverse findings coherently emphasize an essential role of inhibition in shaping neuronal computations.

6.3 General discussion and open questions

Several questions remain regarding the inhibitory switch of plasticity, e.g. whether inhibitory control of dendritic signals indeed operates in the disinhibitory circuits of the brain, whether inhibition modulates plasticity in a pathway-specific manner, and why there is a dichotomy in time scales between proximal and distal dendritic areas. I will first address these open questions and then turn to an in-depth discussion about inhibitory plasticity as a biologically plausible mechanism to fine-tune feedforward circuits. Before concluding, I will critically assess the robustness of the proposed mechanism.

6.3.1 Disinhibitory control

As already suggested, the mechanism investigated in this thesis fits well into the recently emerging picture that disinhibitory circuits are involved in learning. In the following, I will substantiate this claim by arguing why I think that the mechanism presented here indeed underlies the effects of disinhibition on learning, then I will highlight the relevance of disinhibitory control. Finally, I will point out unresolved issues regarding the types of interneurons that receive modulation during learning.

Do disinhibitory circuits employ the cellular mechanism explored in this thesis for plasticity control? In this thesis, we analyzed how inhibition can modulate plasticity directly, by gating dendritic signals (such as bAPs and calcium spikes). We argued that this mechanism likely plays a role in the recently studied disinhibitory circuits that contribute to learning. However, (dis-)inhibition in these circuits could alternatively modulate plasticity indirectly, simply by altering neuronal firing rates. However, the following computational arguments and experimental results support that the targets of disinhibitory control are dendritic signals.

First, the mechanism explored here is more appealing due to its computational features: (i) the all-or-none nature of dendritic spikes allows for a switch-like modulation of plasticity, in contrast to a gradual change in firing rate, (ii) the compartment-specific control of dendritic spikes enables pathway-specific control of plasticity, which cannot be achieved by a global change in postsynaptic response, and (iii) the dynamic and transient nature of dendritic feedforward inhibition preserves forward-directed information processing and neural selectivity.

Second, experimental studies support that the mechanism of disinhibitory control involves modulation of dendritic signals. On the one hand, interneurons with distinct dendritic targets, such as somatostatin (SOM)- or parvalbumin (PV)-positive interneurons, are inhibited during learning (Fu et al., 2015; Letzkus et al., 2011; Wolff et al., 2014); while PV interneurons target peri-somatic regions and are hence well suited to modulate either (bAPs or firing rate), SOM interneurons target more distal dendrites and therefore modulate dendritic spikes rather than firing rate. On the other hand, pyramidal neuron selectivity was mostly conserved when disinhibitory circuits were activated (Atallah et al. (2012); Fu et al. (2014); Niell and Stryker (2010); Wilson et al. (2012), but see El-Boustani et al. (2014)), while the somatic response was gain-modulated. These observations could be explained by inhibition of BAC firing (via inhibition of bAPs or calcium spikes), which changes the gain but not the tuning. However, dendritic activity remains to be recorded during disinhibitory manipulation in learning experiments.

Taken together, there is strong evidence that disinhibition controls learning by modulating dendritic signals. It may however be that ultimately the change in firing rate– caused by modulation of dendritic signals – determines plasticity.

When is the disinhibitory switch utilized? During the course of this thesis, we have already argued in depth that in adult brains, where abundant inhibition limits plasticity, disinhibition that switches on plasticity during behaviorally relevant conditions is an elegant solution to the plasticity-stability dilemma. The mechanism could, however, be relevant beyond this function, as it may also operate in developing brains. During

a critical period in early lifetime, the brain is highly plastic. The reason for this could simply be that principal neurons receive less inhibition in general, or that principal neurons are tonically disinhibited. It is well established that inhibition typically matures only after birth (Huang, 2009), which may keep inhibition levels low initially. However, tonic disinhibition may become relevant during later phases of the critical period. A recent study shows that critical period plasticity requires nicotinic acetylcholine receptors and ends when inhibitors of those receptors are upregulated (Morishita et al., 2010), supporting this view. An inhibitory switch of plasticity could hence serve important roles during a diversity of conditions, ranging from slowly changing stages of development to rapidly changing states of the organism. More experimental data for each condition is needed to grasp the behavioral implications of disinhibitory circuits. Although we do not yet know the diversity and combinatorics of inhibitory switches themselves, some of the variety seems to be unfolding, as I will discuss next.

Are disinhibitory circuits functionally specific? Although disinhibitory circuits with similar architecture could be identified in a range of areas, experimental results about the dynamics of disinhibitory circuits during learning partly differ when it comes to which interneuron type is inhibited. Both SOM and PV interneurons have been shown to be important for learning in fear conditioning paradigms (Letzkus et al., 2011; Lovett-Barron et al., 2014; Wolff et al., 2014). In auditory cortex and amygdala, both types were inhibited during mild electrical shocks to the animal's feet (foot shocks, unconditioned stimulus, Wolff et al., 2014). In the hippocampus, however, foot shocks quite surprisingly *activated* SOM interneurons (Lovett-Barron et al., 2014). One might conclude from this that the dendritic compartment that needs to be released from control during learning differs between areas. However, we need to be cautious when drawing conclusions from so few experimental studies, as a myriad of other factors could be involved. One may nevertheless speculate that where inhibition is released depends on the involved pathways: while sensory information arrives on more proximal dendrites in cortex, it arrives via the perforant path in the hippocampus (Spruston, 2008). Only recently it became possible to study the selectivity of single synapses (Chen et al., 2011). Using this approach to determine the functionality of dendritic inputs during fear conditioning experiments, one could subsequently assess how the optogenetic manipulation of different interneuron classes influences synaptic plasticity of the classified synapses, and the behavioral performance of the animal. The resulting data could elucidate the functional specificity of disinhibitory circuits in different areas.

In general, the functional roles of interneurons and their control in different areas during different task conditions need further investigation.

6.3.2 Gating bAPs and calcium spikes in a pathway-specific manner

As mentioned in the last section, different inhibitory switches – involving different interneuron types that differ in their dendritic targets – may combine in various ways. In this section, I will argue that a pathway-specific modulation is a feature that creates the combinatorial potential for inhibitory switches.

First, pathway-specific control is a good trade-off between circuit simplicity and fine regulation, because it provides a simple switch for all synapses of a pathway and at the

same time enables differential control over distinct functions. For instance, bottom-up (sensory) and top-down (intra-cortical) inputs arrive via different pathways in L5 and CA1 (Larkum, 2013; Lovett-Barron et al., 2014). In a supervised learning setting, where the goal is to learn a target, it is desirable to adjust bottom-up feedforward processing without altering top-down feedback connections (target). Transferring synaptic configurations from one pathway to the next, for purposes of memory consolidation, also requires stability of one, but plasticity of the other pathway. Note that an individual control opens the possibility to dynamically switch roles between pathways, e.g. depending on task condition. Finally, proximal and distal pyramidal neuron dendrites receive inputs from distinct pathways and modulation from distinct interneurons, which is useful for pathway-specific computations. Experiments additionally demonstrated that PV interneurons inhibit SOM interneurons (Lovett-Barron et al., 2012; Wolff et al., 2014), which enables a switch from distal to proximal inhibition, depending on the input to the circuit (Wolff et al., 2014).

Beyond pathway-specific switches of input and plasticity, it seems that proximal and distal areas of the dendritic tree operate on different time scales. First, proximal synapses can undergo STDP as they are readily reached by bAPs. Distal plasticity, however, depends on dendritic spikes and hence less on precise timing than STDP, because dendritic spikes have much longer time constants than sodium spikes (Antic et al., 2010). Second, due to the nature of the underlying depolarizations, proximal plasticity needs to be precisely timed in contrast to modulation of distal plasticity (Wilmes, Sprekeler, Schreiber, 2016). Also, proximally targeting fast-spiking PV interneurons are involved in stimulus-triggered precisely delivered feedforward inhibition, while distally targeting SOM interneurons can also be sustainedly activated by feedback and long-range connections (Tremblay et al., 2016). Taken together, pyramidal neuron dendrites seem to support spatially segregated forms of information processing that operate on different time scales. The mechanism to achieve precise timing of proximal inhibition, proposed in this thesis, will be discussed thoroughly in the following.

6.3.3 Inhibitory plasticity to learn a selective gating of bAPs

In the second study (Wilmes, Sprekeler, Schreiber, 2016), we proposed an inhibitory STDP rule that could shape feedforward inhibitory circuits such that they learn the tight timing to inhibit bAPs. It is however unclear how the rule could be implemented biologically. In the following I argue that our assumptions for the rule are not biologically unrealistic and discuss the conditions under which the rule could be realized. In a second step, I will assess further ingredients necessary for the rule to function, such as an inhibitory feedforward architecture, or the availability of inhibitory synapses.

How could the iSTDP rule be implemented biologically?

To evaluate whether the proposed iSTDP rule could be biologically implemented, one has to take into consideration that the rule is a function of the relative timing between postsynaptic (b)AP and activation of the inhibitory synapse. The question then is how the combination of the two factors can trigger either potentiation or depression of the active synapse, dependent on their relative timing?

Plasticity induction in general, and at inhibitory synapses in particular, is not well understood. Among many other factors, inhibitory plasticity depends on calcium elevation (Haas et al., 2006; Holmgren and Zilberter, 2001; Woodin et al., 2003), e.g. mediated by bAPs, and on spike timing (D'Amour and Froemke, 2015; Haas et al., 2006; Holmgren and Zilberter, 2001; Woodin et al., 2003), similar to excitatory synaptic plasticity. Unlike excitatory synapses, inhibitory synapses (in adults) do not contribute to the depolarization needed for calcium elevation, such that the synaptic change cannot be explained by time-dependent nonlinear summation of bAPs and postsynaptic potentials.

The solution to the problem might lie within the architecture of inhibitory feedforward circuits, where inhibition is accompanied by excitation, such that EPSPs and IPSPs follow each other closely in time. Hence, EPSPs and the bAP could provide the calcium levels required for inhibitory synaptic change. To achieve spike-timing dependence, inhibitory synaptic activation needs to influence the induction of plasticity via a different intracellular pathway.

For instance, the proposed rule could be implemented assuming that (i) inhibitory synaptic activation is required for induction, and (ii) calcium elevation at the time of inhibitory synapse activation determines synaptic change as follows: synaptic activation during low calcium elevation leads to LTD while during high calcium elevation it leads to LTP. The consequence would be that an inhibitory synapse active during EPSPs (slow and little increase in calcium), gets depressed, while one active during the bAP (fast and strong increase in calcium), gets potentiated. Hence, synapses that can interfere with the EPSP are punished and those that can selectively block the bAP (as they activate only after an AP was generated) are rewarded, corresponding to the main characteristics of the proposed rule.

It is less clear what happens to synapses that are too late to have any effect on either EPSP or bAP according to the proposed implementation. As discussed in the second paper of this thesis, the functioning of the mechanism is unaffected by these synapses, demonstrated by the fact that both the schematic and the anti-Hebbian version of the iSTDP rule succeeded. Within the proposed implementation scheme, a synapse that is active after the bAP may be potentiated, if the bAP-mediated strong calcium elevation activated processes for LTP induction that are then directed to the active synapse (anti-Hebbian rule). Otherwise, i.e. if processes for plasticity are only triggered after synaptic activation, such that synaptic change is determined by the declining calcium elevation after the bAP, the synapse may be depressed or stay unchanged (schematized rule), dependent on the time constants of calcium decay.

These speculations are in line with experiments as (i) differing levels of calcium can trigger distinct cellular cascades, leading to LTP or LTD (Malenka and Siegelbaum, 2001), and (ii) timing of inhibitory synaptic activation could enter the equation via the activation of $GABA_B$ receptors, which have been implied to play a role in the induction of inhibitory synaptic plasticity (Komatsu, 1996; Maffei, 2011). Ultimately, however, a better understanding of inhibitory plasticity and its induction mechanisms is required, before the biological plausibility of possible learning rules can be sensibly evaluated. We can however assess how plausible the assumed circumstances are under which the proposed rule operates: an inhibitory feedforward circuit architecture that accommodates inhibitory connections with various activation timings.

How plausible is the assumption that bAPs are canceled by feedforward inhibition?

We investigated whether inhibitory neurons can learn to gate bAPs while assuming that these neurons are embedded in a feedforward circuit motif, where principal neurons are targeted by interneurons that receive the same input. This motif was a natural choice as it ensures a reliable delay between excitation and inhibition in the principal neuron. Additionally, feedforward circuits are extremely abundant in all areas of the brain (Tremblay et al., 2016). Such a ubiquitous motif seems reasonable for a mechanism that should be available to every principal cell. The sheer abundance of feedforward circuits raises the question how they develop. Appropriate spike-timing dependent plasticity rules at all synapses in the circuit may be the solution, as demonstrated by Kleberg et al. (2014) in mircocircuit models where an pool of excitatory neurons projected to a population of principal neurons and to a pool of interneurons that in turn projected onto the principal neurons. They showed that with Hebbian STDP at all excitatory synapses, first principal neurons and interneurons specialize to a subset of excitatory input neurons, and second only those interneurons that specialize to the same input as their postsynaptic targets strengthened with anti-Hebbian STDP of the inhibitory synapses. The availability of disynaptic feedforward inhibition provides a reasonable setting for the proposed mechanism. However, the presence of feedforward inhibition does no guarantee that inhibitory synapses with the appropriate timing exist in the microcircuit.

What if there are no inhibitory synapses with the appropriate timing?

We suggested a learning rule according to which inhibitory plasticity can shape feedforward circuits to achieve the appropriate timing of inhibition. In particular, the learning rule selects appropriately-timed inhibitory synapses from a set of available synapses. However, what if there are no synapses that are appropriately timed? First of all, the architecture of the feedforward circuit increases the likelihood that synapses are equipped with the appropriate timing; it limits the range of possible timings as inhibitory neurons and principal neurons receive the same input. Given the possibility that synapses with the appropriate timing are nevertheless lacking in the feedforward circuit, we should ask whether synapses with an inappropriate timing could *change* to become appropriately timed. Recycling synapses is an elegant solution, because maintaining unused synapses is unfavorable, and creating new synapses is effortful. Activity-dependent myelination (Bakkum et al., 2008; Baraban et al., 2015) could adjust synapses in their timing such that their activity matches the selection criterion of the learning rule. In line with this, a surprisingly large fraction of myelin ensheathes PV interneuron axons (Micheva et al., 2016). If synapses do not undergo any LTP and are deprived of accompanied growth factors, they might adjust their axonal delays, until they match the selection criterion, i.e. until they fall into the potentiation window of a learning rule. Taken together, it is not unreasonable to assume that inhibitory synapses with the right timing are eventually available.

Efficiency of the proposed learning mechanism

Next to being biologically realizable, learning processes ideally should be efficient to be adopted by the brain. As will become clear in this section, there are different aspects to the efficiency of the learning process.

Efficiency can be independent of the particular learning rule. For instance, the suggested learning process requires that the learning rule selects synapses from a pool. Such a process is efficient if it terminates once selection is complete. We highlighted in our second study that inhibition conveniently learns to eliminate its own learning signal, such that the process can terminate if all synapses in the pool receive a common signal for learning. The alternative to a common signal is competition for resources among synapses, imposed e.g. by an upper bound on the sum of synaptic weights. However, in this case learning will terminate, but not immediately after the end of the selection process. Synapses closer to the soma become more potentiated as they experience the bAP even if the bAP is already eliminated further up in the dendrite. The seeming inefficiency could hence be a feature as it selects for synapses that eliminate the bAP earlier. In general, it is unclear whether selection processes need to have an end, or whether synapses in the dynamically changing brain continuously adjust themselves. A selection process that ends once it is completed can be considered resource efficient.

Additionally, the learning rule has a large impact on the efficiency of the learning process. We can assess the efficiency of learning rules in terms of time and resources: (i) Temporal efficiency, the time or number of learning episodes it takes to achieve the learning goal (i.e. to inhibit the bAP) depends on the integral of the learning rule over the optimal time window, i.e. it depends on how strongly synapses with optimal timing are potentiated. However, there is a trade-off, because large weight updates are sensitive to variations in synaptic activity (which could just be noise). (ii) Resource efficiency: rules that only strengthen synapses with a suitable timing are more resource-efficient than those that also strengthen other synapses (e.g. those too late to inhibit the bAP). We can quantify resource efficiency by relating it to temporal efficiency if we compare the temporal efficiency of rules with equally large integrals of the total potentiation domain. If all resources (the total integral) go into strengthening the appropriate synapses, learning is faster. In this sense, the schematic rule or a rule with a similar potentiation integral (like e.g. the modified version of the anti-Hebbian rule introduced in our second study) are efficient. However, less efficient rules, such as the anti-Hebbian rule, could also have advantages: First, robustness: even if synapses with suboptimal timing are favored, which cannot inhibit the bAP by themselves, they can still contribute to the collective effort of the group of synapses – the more synapses contribute, the more robust is the mechanism to failure of individuals. Second, flexibility: if conditions change and a different timing becomes relevant, an inefficient system might adjust faster to the new circumstances. Third, simplicity of implementation: depending on time constants of intracellular signaling cascades, finely timed windows for LTP might be more difficult to realize than broader windows. Of course the sharp transition from LTP to LTD at small positive spike-time differences (Δt) is vital for the rule to work, and such sharp transitions have been experimentally measured. However, a restricted range of timings (instead of a single turning point), might pose totally different challenges to the cellular machinery.

Robustness of the mechanism of learning to gate bAPs

One objection to the proposed mechanism – to learn the right timing for gating bAPs – is that it remains to be tested in a realistic network setting. Challenges the mechanism faces in a network include inputs arriving at high frequency, multiple input patterns that need to be encoded and gated, and most importantly inputs that change.

With regard to high stimulation frequencies, we showed that the mechanism breaks down at ~30 Hz. This implies that it is also less robust in the presence of non-periodic Poissonian input with instantaneously high firing rates. Instead, network oscillations in medium frequency ranges, such as theta, are ideal conditions for the mechanism. Interestingly, neuromodulation controls theta rhythm in hippocampus and its disruption impairs learning and theta rhythm (Hasselmo et al., 2002).

As a part of a larger network, one neuron might participate in multiple cell assemblies and hence should be able to encode various input patterns. Learning a selective gating of bAPs for diverse inputs should be possible in the following sense: for each input pattern, the learning rule selects inhibitory synapses with the appropriate timing, such that a different set of interneurons is recruited. However, bAP control for one input pattern could interfere with the forward-directed processing of another, if different input patterns activate in close temporal proximity.

Most importantly, it remains to be shown whether the mechanism can successfully cope with changing inputs.
(i) The presynaptic input could change in terms of how quickly it drives the postsynaptic neurons, e.g. in terms of strength by switching from regular to burst firing, or frequency. Albeit being conceivable that the feedforward architecture can cope with such changes in input strength and frequency, as both interneuron and principal neuron receive the same changes in drive, this remains to be shown.
(ii) The excitatory synapses could change. The synapses from the excitatory drive to the pyramidal neuron may not change based on STDP as it is under inhibitory bAP control, but due to other mechanisms, such as dendritic-spike mediated plasticity. The synapses from the excitatory input to the involved interneurons could also change. These changes are effective if either all excitatory synapses change in one direction, or few critical synapses change strongly. In the following, I will distinguish synaptic changes with regard to their effects on AP and bAP: On the one hand, if synapses onto the principal neuron strengthen, or synapses onto the interneurons weaken, then the AP occurs earlier relative to inhibition, and the bAP passes. However, this triggers inhibitory plasticity that in turn promotes a different set of inhibitory synapses. On the other hand, synaptic change could lead to a completely silenced postsynaptic neuron: If synapses onto the principal neuron weaken, the excitatory input may not cause a (b)AP because either it might be too weak to drive the neuron per se or inhibition activates before an AP is initiated as AP initiation takes longer the weaker the input. Also, if the synapses onto the interneurons become stronger, inhibition arrives earlier and silences the neuron. In both cases, the inhibitory plasticity rule cannot adjust inhibition due to lacking bAPs. Homeostatic mechanisms, however, could be the rescue, as they can downregulate inhibition as well as spiking- and plasticity thresholds (Turrigiano and Nelson, 2004) in the absence of activity until the cell's activity increases.
(iii) Correlations in the input could change. With excitatory STDP, neurons can become selective to correlated inputs. If two correlated inputs impinge onto the neuron at the

same time, it randomly becomes selective to one of the two (Song et al., 2000), but if the two inputs arrive at different points in time the neuron can learn to react to both. With inhibitory STDP, inhibitory synapses could in principle be fine-tuned to consolidate the excitatory synapses for both inputs independently (see discussion above whether the mechanism can learn to gate multiple input patterns). If one of the inputs becomes less correlated, the pyramidal neuron and the interneuron should stop reacting to that input. The inhibitory synapses tuned for this input should remain until homeostatically downregulated. As for different inputs at different times, a new correlated input should cause the postsynaptic cell to fire, such that inhibition could be tuned to consolidate this input.

Taken together, the robustness of the mechanism under realistic conditions, i.e. whether it allows one cell to process multiple realistic and dynamic input patterns while controling their plasticity, remains to be investigated.

6.4 Conclusion

In this thesis, I highlighted the relevance of inhibitory interneurons for neuronal computations, including their role in regulating excitatory synaptic plasticity and neuronal firing modes. In our studies, we demonstrated that temporally precise inhibition is useful for these objectives and also biologically achievable. Further, this thesis contributes to the understanding of the currently investigated disinhibitory control of learning, which seems to be a widespread and behaviorally relevant mechanism. Ultimately, I would like to emphasize the importance of single neuron computations, especially on the level of dendritic processes, for the proper functioning of neuronal circuits.

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Selbständigkeitserklärung

Ich erkläre, dass ich die vorliegende Arbeit selbständig und nur unter Verwendung der angegebenen Literatur und Hilfsmittel angefertigt habe.

Berlin, den 25.08.2016 Katharina Anna Wilmes